HIPPOCAMPAL CONNECTIONS AND MEMORY: THE MEDIAL SEPTUM AND MAMMILLARY BODIES

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David N. Harper

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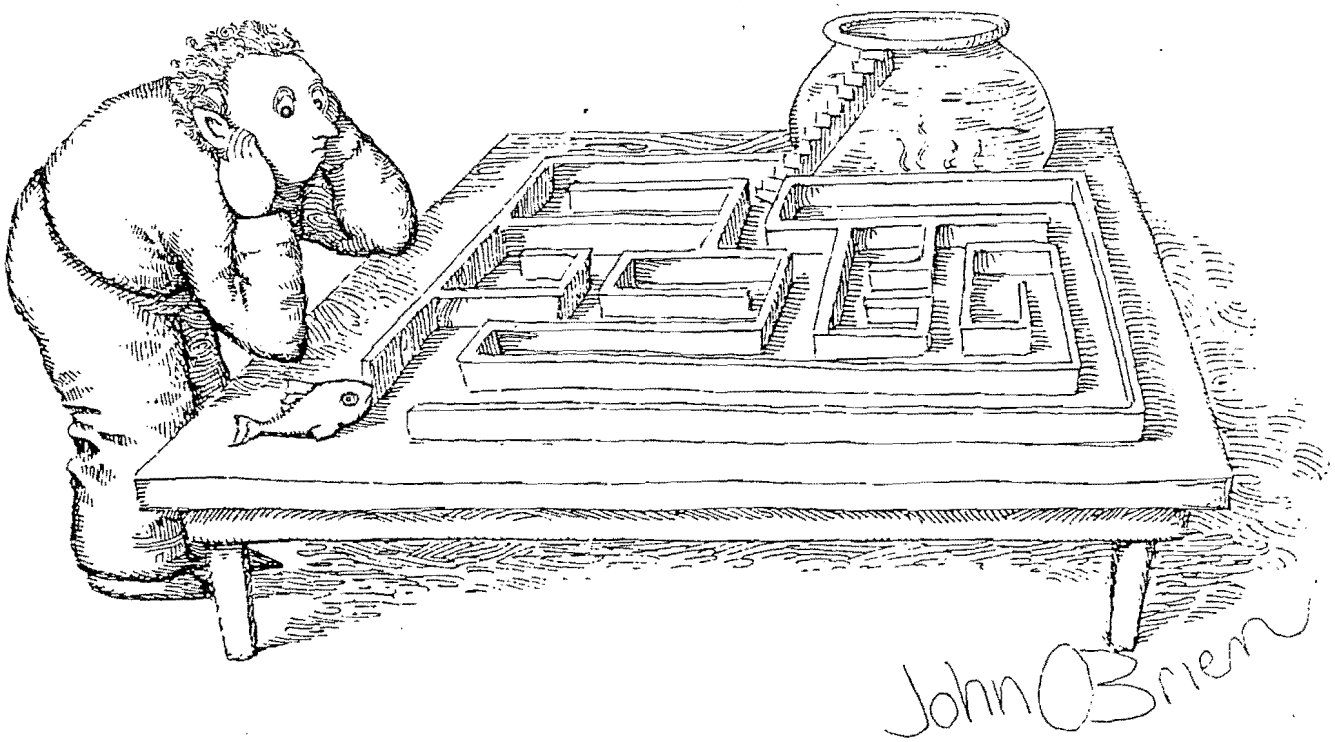

A particularly insightful cartoon given to me by Bob Stark.

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ABSTRACT

There are a number of indications that structures associated with the hippocampal region of the mammalian brain have an important role in memory function. Two regions, the medial septum and mammillary bodies, are of particular interest because of their implication in the memory deficits observed in some human neurodegenerative diseases (e.g. Alzheimer's Disease and Korsakoff's Syndrome) and the effects on memory following experimentally applied damage in non-human subjects. The present research investigated the role of the medial septum and mammillary bodies in memory by assessing the effects of damage in these structures on performance of rats in two types of memory task : Serial-Probe Recognition and Delayed-Matching-to-Sample. These two types of task were chosen because of their ability to allow comparisons with some commonly-used human memory procedures and because of their utility in examining several major issues that have not been adequately addressed in previous research.

The results from the serial probe recognition studies which assessed memory for list items showed that a Serial Position Effect analogous to that observed in humans, i.e. high accuracy at end list positions compared to middle ones, could be produced with rat subjects tested in a 12-arm maze. Mammillary lesions resulted in a loss of the superior accuracy for both early and late list positions, but no significant reduction in accuracy overall. By contrast, medial septal lesions were very disruptive to overall accuracy and also eliminated the superior accuracy at early list positions. However, medial-septal lesioned rats continued to show superior accuracy at late list positions. The pattern shown by the medial septal group was consistent with the pattern observed in Alzheimer's Disease and Korsakoff's Syndrome subjects.

Subsequent studies investigated the effects of Medial Septum and Mammillary Body lesions using an automated delayed-matching-to-sample task. A particular

question of interest in the delayed-matching research was whether the disruptive effects of lesions on performance were the result of a change in the rate at which information is 'lost from memory' or, in the subjects' discrimination of to-be-remembered material in the first instance. This issue was addressed using an analytic separation of delay-independent aspects of performance (accuracy at a zero second delay) from the memorial or delay-dependent aspects of performance (rate of accuracy decline over delays). This separation was achieved by examining performance over a range of delays and utilising a bias-free measure of accuracy (Davison & Tustin, 1978) fitted by a quantitative model of memory performance (White & McKenzie, 1982). The results of the delayed-matching studies showed that large medial septal damage, but not mammillary damage or small medial septal damage, produced an increase in the rate of forgetting without a change in the delay-independent aspects of performance.

In addition to examining lesion effects on the basic delayed matching task, a systematic investigation was conducted of the interaction between these lesion effects and interference from proactive (behavior and stimuli occurring prior to the current trial) and retroactive sources (behavior and stimuli occurring during the delay of a current trial). This investigation was prompted by indications that Alzheimer's and Korsakoff's subjects display heightened susceptibility to these sources of interference. A heightened susceptibility to proactive interference from previous trials in the large medial septum lesion group was consistent with, and may have been the cause of, the increase in rate of forgetting and the reduction in serial probe recognition accuracy observed in this group. However, the investigation of interference effects also resulted in several findings that were hard to reconcile with other findings. For example, retroactive interference, while not having a differential effect across lesion groups, had an unexpected influence on the delay-independent measure of performance but not on the delay-dependent measure.

The consistency of the present findings with human and nonhuman research is discussed. It is concluded that the medial septal region plays an important role in mnemonic function and that damage in this area produces an increased sensitivity to proactive interference effects.

Chapter 1 INTRODUCTION

Among the many behaviors which may reflect cognitive activity in an organism, 'memory' has long been a topic of interest, and a major scientific endeavour has been the attempt to understand memory function at both the behavioral and neurological levels of analysis. A considerable body of evidence now exists which has indicated that structures associated with the hippocampal formation region of the mammalian brain have an important role in memory function. Two regions, the medial septum and mammillary bodies, are of particular interest because of their implication in the memory deficits observed in some human neurodegenerative diseases (e.g. Alzheimer's Disease and Korsakoff's Syndrome) and the effects on memory following experimentally applied damage in non-human subjects. The present research investigated the role of the medial septum and mammillary bodies in memory by assessing the effects of damage in these structures on performance of rats in two types of memory task : Serial-Probe Recognition and Delayed-Matching-to-Sample. These two types of task were chosen because of their ability to allow comparisons with some commonly-used human memory procedures and because of their utility in examining several major issues that have not been adequately addressed in previous research.

Research studies on the neurological bases of memory have historically been guided by several major assumptions. One assumption implicit in much of the research is that a greater understanding of human function will be achieved if we treat behavior as a dependent variable which is the product of both physiology and the environment. The rather complex task that therefore confronts researchers is to examine the effect of alterations in both the physiology and environment on those behaviors which may be subsumed under the title of 'memory'. A second major assumption present in many studies is that memory function can be studied in a wide range of species. Given the obvious phylogenetic importance of retaining information, it is not surprising that all animal species exhibit behaviors which indicate the existence of memory. Thus, with the observations we make in one species we may gain strong indications of memory

function in other species, and what we learn about memory function in nonhumans may be of direct relevance to understanding memory function in humans. A final assumption present in a number of studies investigating memory is that we can learn about normal memory function by disrupting it. For example, a rat may be given a brain lesion or may have new stimuli placed in its environment in order to assess the disruptive effects on performance in a memory task. The examination of behavior under conditions of disruption is a common approach in many scientific endeavours. For instance, in ergonomics, which explores human / machine systems by examining the conditions in which they fail, a study may assess the road accidents which occur when different road sign designs are used. However, while exploring memory function by examining it under abnormal conditions is a useful approach, it is of course but one approach and has its limitations. Ultimately it will be through an integration of the evidence supplied by various research avenues that we will come to understand memory function more fully.

Despite the general acceptance of various assumptions implicit in the research, our knowledge is far from being integrated into a complete and congruent understanding of memory function, partly because of the wide diversity of methods and interpretations of the data. To arrive at a greater understanding of memory, the data generated by researchers needs to be integrated. However, the integration of research data has been restricted by differences between researchers in their approaches to scientific enquiry. One type of data explanation involves the use of hypothetical constructs and mechanisms to account for data. Another approach is to postulate empirical laws or principles, with very little reference to hypothetical constructs. The value and weaknesses of both approaches has been argued by a great number of authors (see Skinner, 1963, 1966; Neisser, 1967). Although no attempt will be made here to evaluate the two approaches, it should be noted that the approach traditionally preferred by researchers who investigate memory in non-human subjects is the analytic approach with very little reference to hypothetical constructs (Wright & Watkins, 1987), whereas memory research with human subjects abounds with hypothetical constructs

(e.g. Brown, 1958; Atkinson & Shiffrin, 1968). Therefore, it is not surprising that human and nonhuman memory research has proceeded somewhat independently of each other until perhaps the last 10 years. Unfortunately this separation of research traditions has resulted in problems when it comes to drawing together various lines of scientific evidence. Thus, a positive research trend has been the increasing amount of comparison drawn between the results obtained using different subject groups, species and techniques. The present research like much of that now being undertaken attempted to examine issues and provide data compatible with an integration with other relevant research. Ultimately such an approach is desirable if we wish to increase our understanding of memory function at both the behavioral and neurological levels.

In the attempt to further our knowledge about the neurological bases of memory and to integrate several lines of evidence, the present research investigated the potential role of two brain regions in memory - the medial septum and the mammillary bodies. There are two general areas of research that suggest that both the medial septal and the mammillary body regions of the brain are important in memory function: clinical research on humans with neurodegenerative disorders and human and non-human experimental research exploring the neurological bases of memory. Both lines of research provide converging support for the possibility that an indepth examination of the role of medial septal and mammillary body regions in memory will be of value. The relevant research is discussed in the following sections.

1.1 TWO NEURODEGENERATIVE DISORDERS - ALZHEIMER'S DISEASE AND KORSAKOFF'S SYNDROME

Alzheimer's Disease (AD) and Korsakoff's Syndrome (KS) are two human neurodegenerative disorders that are characterised by a variety of memory disruptions. Both disorders are of interest because although they differ in their epidemiologies, they display a number of similarities at both the cognitive and neurological level. The observed neuropathology and disruptions to memory function in these disorders indicates that brain structures connected to the hippocampal formation may play important roles in memory performance. In particular, the medial septal region is implicated in both AD and KS, whilst there is considerable support for a role of the mammillary bodies in KS. In Section 1.1.1 the memory disruptions that take place in AD and KS will be discussed. This is followed by a discussion, in Section 1.1.2, of the important neurological changes in the two diseases which may underlie these memory disruptions.

1.1.1 Memory Disruptions in Alzheimer's Disease and Korsakoff's Syndrome

AD and KS differ from one another in their etiology. AD is the most common form of dementia associated with the elderly and is having a greater impact on society as the average lifespan increases. Jorm, Korten & Henderson (1987) carried out a review of 47 studies and concluded that the prevalence of AD in men and women increased with age according to an exponential model, with a doubling of rates every 5.1 years. AD is progressive, irreversible, and there is a great deal of debate over it's cause(s). A number of causal factors have been suggested, such as heredity (Mortimer, 1990), prior head trauma (Mortimer, French & Hutton,1985), aluminium intake (Crapper, Krsihnan & Dalton, 1973), use of analgesics (Murray, Greene & Adams, 1971) and thyroid disease (Heyman et al., 1984), (and has been recently reviewed by Henderson, 1990 and Mortimer, 1990). KS is a disorder which is most commonly seen in alcoholics, but not confined to them. However, for the present discussion only alcohol related KS will be discussed. Traditionally, KS was attributed to a deficiency in

thiamine (vitamin B1) because of poor diet in severe alcoholics. For example, animals and humans deprived of thiamine show clinical features and various aspects of neuropathology associated with KS, and these symptoms can be alleviated with thiamine administration (Brierly, 1977). However, a number of studies suggest that the symptoms and neuropathological features of KS may also arise because of the neurotoxic effects of alcohol. For example, feeding rats nutritionally balanced diets, but containing alcohol, results in a variety of memory disruptions and limbic system damage in the brain (e.g. Freund, 1970; Riley & Walker, 1978; Arendt et al., 1989). Therefore, it may be the combination of both a thiamine deficiency and long-term alcohol intake that are responsible for KS. Whatever the causes of both AD and KS they are of considerable interest to behavioral neuroscientists because of their effects on cognitive functioning.

There are a number of similarities in the memory impairments observed in both AD and KS. In AD most aspects of memory are implicated - including remote memory, i.e. memory for events occurring prior to the disorder (e.g. Corkin et al., 1984), as well as episodic & semantic memory, that is memory for specific past events and memory for previously acquired knowledge and meaning (e.g. Weingartner et al., 1983). Like AD, KS results in a variety of similar memory problems (Delis et al., 1991; Butters, 1985). For instance, KS subjects also show poor remote memory (Albert et al., 1982) and impairments in episodic and semantic memory tasks, although some differences exist between AD and KS subjects depending on the stimuli used to assess semantic memory (Butters et al., 1987).

Although AD and KS sufferers display a variety of similar memory disruptions, some of the most severe disruptions are observed in tasks which assess the shorter-term aspects of memory; it is these tasks that are of interest in the present research. Two tasks which have frequently received attention by neuropsychologists working in this area include - memory for items in a list in order to examine changes in the

'primacy' and 'recency' effects, and versions of delayed conditional-discrimination tasks to assess rate of forgetting and susceptibility to interfering events.

Memory for List Items

Both AD and KS result in a disruption to memory for items presented in a list. When presented with a list of items to remember, normal human subjects show superior recognition or recall for items at the beginning (the 'primacy' effect) and end (the 'recency' effect) versus items from the middle of the list (e.g. Murdock, 1962; Glanzer & Cunitz, 1966; Wright et al., 1985). However, the primacy effect is consistently absent in humans suffering from AD or KS. For example, Miller (1971) presented 14 AD subjects with lists of 12 common words and assessed how many words they could then recall. Figure 1.1 (left panel) shows the results from Miller's (1971) study which indicated that the primacy effect was entirely absent in the AD group. However, Figure 1.1 also shows that a recency effect was retained because recall remained superior at late serial positions relative to earlier ones, although recall was reduced at all serial positions.

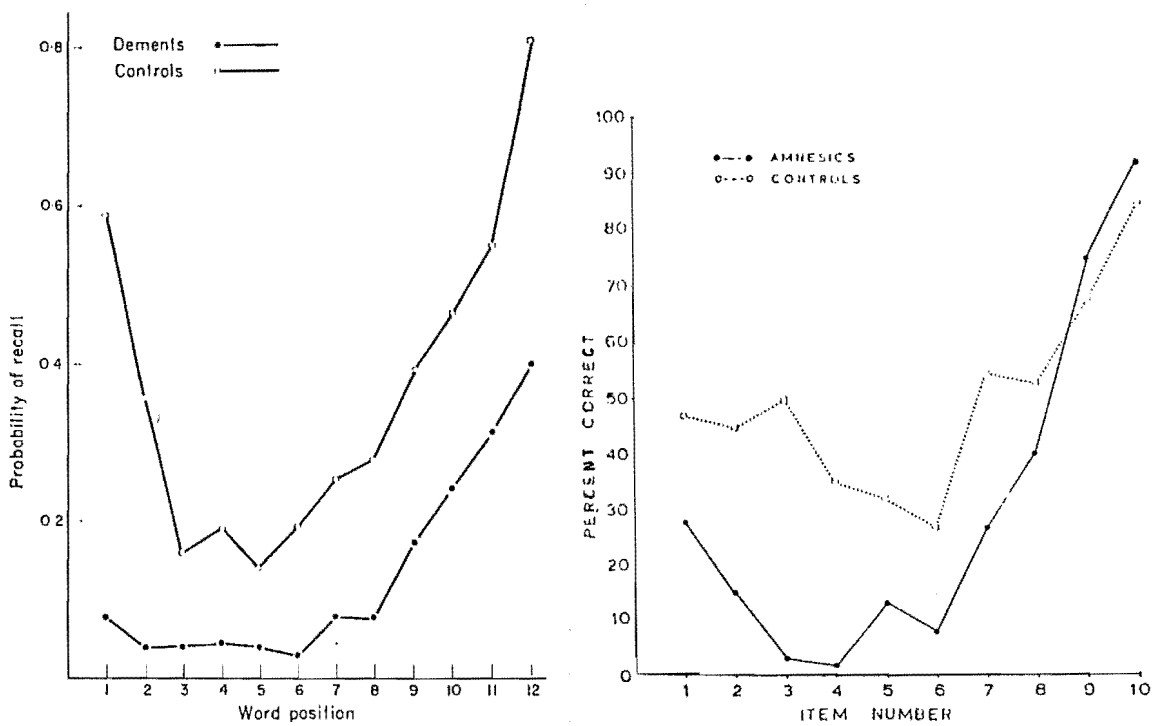

FIG 1.1 Memory for list items for AD subjects - left panel (from Miller, 1971), and KS subjects - right panel (Baddeley & Warrington, 1970). Serial position of list items is given on the x-axis, and percentage of items recalled is given on the y-axis.

The absence of primacy but retention of recency in AD subjects has also been demonstrated in tasks using visual as well as verbal stimuli (Gibson, 1981) and with a serial probe recognition task rather than free recall (Adelstein, Kesner & Strassberg, 1992). It should be noted that this pattern of impairment has been shown with mild AD subjects; in severe AD there is generally poor performance at all serial positions (Adelstein et al., 1992). Similar to mild AD subjects, KS subjects show a greater reduction in recall for items from the early and middle portions and a relatively intact recency effect. Figure 1.1 (right panel) shows the results from Baddeley & Warrington (1970) in which 6 amnesic subjects, 4 of whom had KS, were given a list of 10 nouns to remember. The relative amount of impairment in both disorders is hard to assess because of the methodological differences between the various studies, but both disorders are similar in that subjects show a greater disruption of primacy than recency components when given a list of items to remember.

Delayed Recognition and Recall

Apart from impairments in memory for list items, both AD and KS subjects also show deficits in various delayed conditional discrimination procedures. For example, recognition deficits have been observed in various delayed-matching-to-sample (DMTS) tasks. Although the specific nature of DMTS tasks varies from study to study, generally the following sequence of events occurs in a given trial: a stimulus is presented for a period of time; the stimulus is then removed and a delay period begins; at the end of the delay the subject is presented with the original stimulus and at least one other, and has to identify the original target stimulus. Despite requiring recall rather than recognition, the Brown-Peterson recall task for verbal material and various other nonverbal recall tasks are similar to DMTS in that they also provide methods to assess the rate of forgetting over a relatively short period of time. However, although the research to date with these memory tasks has shown that AD and KS subjects are impaired relative to controls, the exact nature of the impairment is still currently unclear. Some of the research discussed below indicates that the deficit in both disorders may be best characterised as a greater rate of forgetting (i.e. delay-dependent), whilst other

studies indicate that the performance impairments may be constant across delays (i.e. delay-independent).

A number of studies have shown that although AD subjects can perform as well as control subjects when no delay is imposed, there is poorer performance in AD subjects once a delay is present between presentation of a stimulus and subsequent recognition. For example, Hart, Kwentus, Harkins & Taylor (1988) presented subjects with 130 slides of common objects during a study phase and then tested recognition for items immediately after, 10 min after and at 2 and 48 hrs after presentation. They found that although AD and controls performed at around 90 percent with no delay, over the period of 10 min the AD group showed a very rapid rate of forgetting compared to controls. Thereafter, the rate of forgetting in the AD group was the same as that of controls for delays longer than 10 min. Further evidence for the greater rate of forgetting in AD compared to controls over a short delay comes from two other studies: In one study by Sahakian et al. (1988), subjects were presented with complex abstract patterns to remember up to a period of 16 s. Although control subjects showed very little reduction in recognition over the 16 s, AD subjects showed a rapid and systematic decrease in accuracy as delay increased to 16 s. Figure 1.2 (left panel) shows the greater rate of forgetting in the AD group relative to controls with the DMTS task in Sahakian et al's study. In the study by Flicker, Bartus, Crook & Ferris (1984), subjects were presented with a lit panel on a grid and after a delay of 0 to 120 s had to then point to the original panel. Flicker et al. found that between 0 and 2 s delay there was extremely rapid forgetting in mild and severe AD subjects, although the mild AD subjects performed as well as young and old controls at 0 s. Over greater delays the decay in accuracy shown by each group quickly reached asymptote.

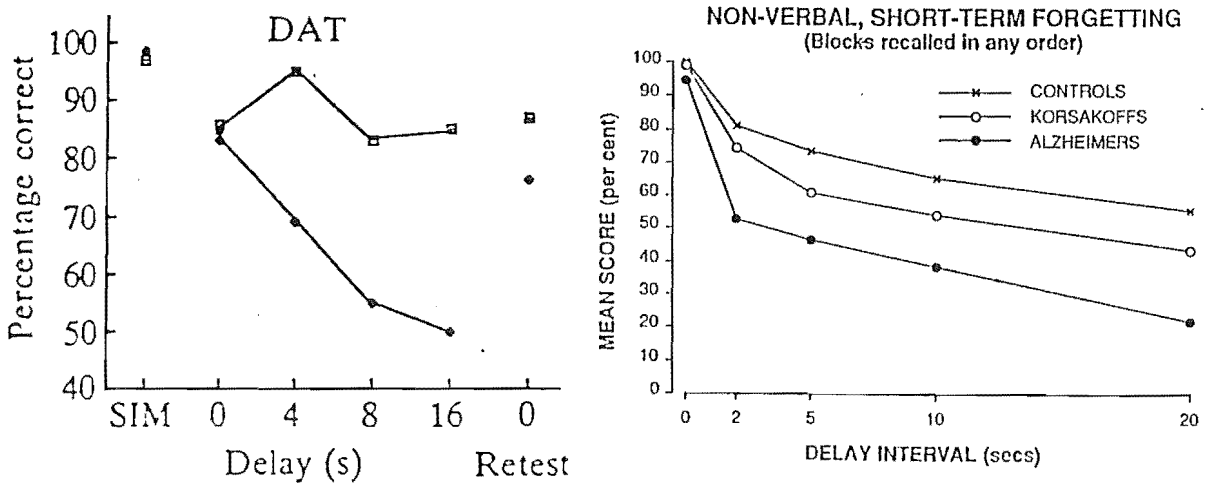

FIG 1.2 Short-term forgetting in AD and KS subjects. The left panel shows results from Sahakian et al. (1988) in which AD (squares) and control subjects (diamonds) were compared using a DMTS task using complex pictures as stimuli. The right panel shows results from Kopelman (1991) in which both AD and KS subjects were compared with controls on performance in a DMTS task in which corsi blocks were used as stimuli. The x-axis on both graphs shows the length of delay between presentation and recognition test. ('SIM' on the left graph's axis is data from simultaneous presentation and testing of performance). The y-axis on both graphs shows the percentage of correct recognitions.

As with AD subjects, there is evidence that KS subjects also show a higher rate of forgetting over a short delay period. In one of the few studies comparing AD and KS subjects on memory task performance over a range of delays, Kopelman (1991) provided evidence for a greater rate of forgetting in both AD and KS relative to controls. Kopelman (1991) required AD and KS subjects to recall a sequence of 2 or 3 blocks from an array of 9 blocks by touching them. KS, AD and control groups all showed levels of recognition (i.e. ability to pick out the original stimulus blocks, irrespective of sequence) at between 95-100 percent when no delay was present. Over the delay period of 0 to 5 s KS subjects forgot more quickly than controls, and AD subjects forgot more quickly than KS. Figure 1.2 (right panel) shows the results for all three groups in Kopelman (1991). The finding of an obvious impairment in KS subjects by Kopelman (1991) using nonverbal material is consistent with the findings of many other delayed recall and recognition studies (e.g. Cermak, Reale & De Luca,1977; Oscar-Berman &

Bonner, 1989). For example, Oscar-Berman & Bonner (1989) presented KS subjects with simple visual stimuli to remember (e.g. green vs red lights) in a delayed-nonmatching-to-sample (DNMTS) procedure. Although their control and alcoholic subjects displayed no reduction in recognition accuracy up to 30 s, the KS group displayed a clear reduction in accuracy over the same period.

In accord with the findings of the DMTS and delayed recall studies discussed above, the results of a number of studies have indicated that for both AD and KS subjects there is a significantly greater rate of forgetting for verbal material when the Brown-Peterson task is used. The Brown-Peterson task involves the presentation and subsequent recall of verbal material after a short delay, during which a distraction task is performed. An example of the Brown-Peterson task can be seen in the study by Kopelman (1985) which involved the presentation of 3, 3-lettered words for 2 s each on any given trial. After a 0 to 20 s delay, during which the subject had to count backwards from 100, the words were recalled. Kopelman found a weak (nonsignificant) indication that there was a greater rate of forgetting in the KS group compared to controls. However, the rate of forgetting for the AD group clearly diverged from the other groups. Although the results from Kopelman (1985) only showed a clear deficit in the AD group, a substantially greater number of studies have found impairments in KS subjects when using the Brown-Peterson task. For example, Cermak, Butters & Goodglass (1971), Kinsbourne & Wood (1975) and Mair, Warrington & Weiskrantz (1979) have all found substantially higher rates of forgetting for KS subjects in the Brown-Peterson task using consonant trigrams (e.g. CGH), word triads or single words compared to control and non-KS alcoholic groups. Figure 1.3 (right panel) shows the performance for KS, alcoholic and control subjects for recall of word triads from the study by Kinsbourne & Wood (1975). Similar to the results obtained with KS subjects, several studies have reported a higher rate of forgetting in AD subjects compared to age-matched controls when using the Brown-Peterson task (e.g. Corkin, 1982; Sullivan, Corkin & Growdon, 1986; Morris, 1986). Figure 1.3 (left panel) shows the greater rate

of forgetting apparent in the Brown-Peterson task with AD subjects relative to controls from Morris (1986).

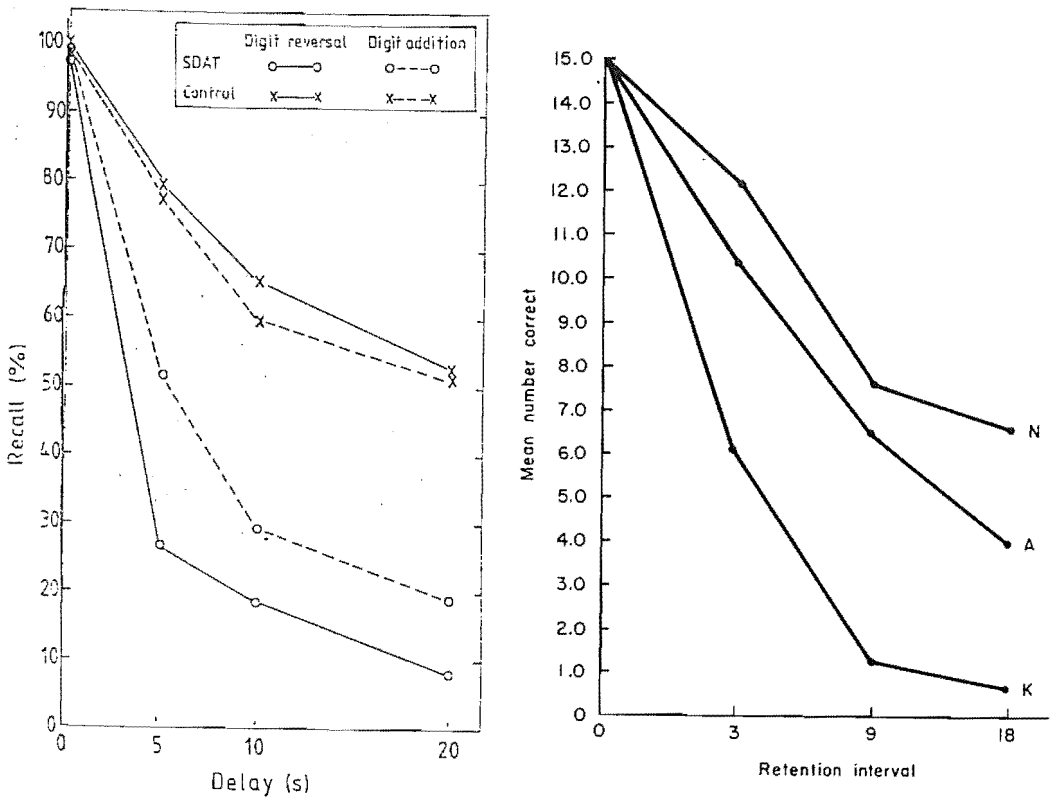

FIG 1.3 Shows performance on the Brown-Peterson recall task for AD subjects - left panel (from Morris, 1986) and KS subjects - right panel (from Kinsbourne & Wood, 1975). The left panel shows performance of AD ('SDAT') subjects versus age-matched controls for percentage of consonant trigrams recalled under two conditions of delay distraction task - digit reversal and digit addition. The right panel shows performance of KS ('K'), non-Korsakoff's alcoholic ('A') and control ('N') groups for number of word triads recalled. On both graphs, delay (in sec.) is given on the x-axis.

Despite the results of a number of studies indicating greater rates of forgetting in AD and KS several researchers have suggested that the deficit is not one that is delay-dependent, i.e. the rate at which performance declines, but rather a deficit in terms of delay-independent processes such as the ability to 'encode' or 'retrieve' material. For example, using a DMTS procedure Money, Kirk & McNaughton (1992) presented AD subjects with a circle, and then after a delay of .01 to 32 s they were required to choose

the original circle from two that differed in size from one another. An advantage of Money et al's study was the use of a model fitted to their data (White & McKenzie, 1982) in order to gain a quantitative measure of forgetting rate. The conclusions of many memory studies are open to a number of interpretations because of the manner in which forgetting rates are assessed (e.g. by visual inspection of slopes, or conducting an ANOVA to demonstrate an interaction of accuracy by condition). Such comparisons are problematic because memory does not appear to decay in a linear fashion and performance in the groups being compared may not share the same level of performance at a delay of 0 s. An empirically validated quantitative model fitted to data can provide a single measure that can be used to assess and compare forgetting rates. Money et al. (1992) fitted White & McKenzie's (1982) negative-exponential decay model, which contains an empirically estimated rate of decay parameter, to their data and found that there was no difference in the rate at which accuracy declined over delays between AD and control subjects. Rather, there was consistently lower performance at each delay in the AD group relative to controls. Therefore, they claimed that the difference was delay-independent in terms of an impairment in initial encoding or retrieval of information.

There are a number of possible reasons for the differences, in terms of how best to characterise the memory impairments, which have emerged between studies examining various human subject groups. First, the absence of a greater rate of forgetting for AD and KS subjects observed in some studies may be because of differences in stimuli used, for example complex patterns in Sahakian et al. (1988) versus circles in Money et al. (1992). Second, a pervasive problem in all studies that have investigated rate of forgetting in AD and KS subjects concerns the choice of the measures used to assess performance. Typically, researchers have used percent correct, or the log ratio of correct responses over errors (Money et al., 1992). However, these measures are not 'bias free'. That is, they do not take into account the distinction often made in psychophysics of 'true' errors, as opposed to a bias to favour one response over another that is independent of the ability to detect or remember that

stimulus (Stubbs, 1976). It may be that differences in performance between some studies occurs because of the presence of greater bias in a subject group, perhaps as a function of stimulus type and/or delay. For example, Kramer et al. (1988) found that compared to controls, AD subjects displayed high levels of bias in terms of a tendency to answer 'yes' when asked if they had seen a particular stimulus item before. Also, this response bias increased as delay between initial item presentation and subsequent recognition increased. Such tendencies will tend to confound the assessment of actual ability to remember. Furthermore, the confounding influence of response bias would tend to be a greater problem in DMTS studies which repeat stimulus items over a number of trials and delays (e.g. Money et al., 1992; Sahakian et al, 1988).

One criticism which applies to many of the studies which have shown a rapid forgetting rate in AD and KS is that most of the evidence for this greater rate of forgetting comes from a divergence in forgetting rates between 0 s and the first delay interval only. Indeed, the rate of forgetting from the first delay onwards often reveals very similar rates between groups (see Figures 1.2 and 1.3 for example). In addition, subjects typically show performance of between 95 and 100 percent when there is no delay. Such high levels of performance can pose a serious problem because the typical unit of measurement is percent correct, and at the upper levels this measure is bounded and thus any differences in performance between groups may not be revealed. Thus in many studies it is unsure whether the greater rate of forgetting observed in a group is partly or wholly the product of the measurement scale.

Apart from high levels of performance at no delay causing problems if performance is measured in terms of percent correct, the existence of such levels of performance are indicative of a serious confound in many studies which have examined the rate of forgetting. Specifically, high levels of performance at no delay may be because the memory task at this point is essentially different to the memory task when a delay is present. In a large number of studies the memory task is different once a delay is present because of the use of distractor tasks only during the delay period to prevent

rehearsal. Morris (1986) and Sullivan et al. (1986) have both shown that in a delay without distraction there was only minimal forgetting in an AD group, but extreme forgetting once a distractor task was required. Therefore, the existence of a greater rate of forgetting may be dependent upon the use of a distractor in studies employing recall and Brown-Peterson tasks (e.g. Kinsboune & Wood, 1975; Mair et al., 1979; Flicker et al., 1984; Morris, 1986; Sullivan et al., 1986; Kopelman, 1992).

Both the use of percent correct measures of accuracy when accuracy is high and the use of distractor tasks in the delay (when data in the no delay condition is also included in the analysis of forgetting rate) may restrict the emergence of group differences when no delay is present and thereby artificially create a difference between groups in the forgetting rates between 0 s and the first delay. However, this second criticism does not apply to studies which have demonstrated a greater rate of forgetting in which a distractor task was not used (e.g. Sahakian et al., 1988; Hart et al., 1988; Oscar-Berman & Bonner, 1989). Therefore in summary, a few studies have shown a convincing demonstration of an elevated rate of forgetting over a relatively short time span, specifically Sahakian et al. (1988) using AD subjects and Oscar-Berman & Bonner (1989) with KS subjects. The remaining studies (if the data between 0 s and the first delay are ignored), tend to support the conclusion that there is a constant (delay-independent) impairment across delays between KS or AD subjects relative controls. Thus, at this point in time, although both AD and KS subjects are significantly and similarly impaired in various delayed recall and recognition tasks it remains unclear exactly how this impairment may be best characterised.

Sensitivity to Interference

A further similarity between the memory alterations in AD and KS is in terms of a heightened sensitivity to various forms of 'interference'. From the research discussed above, it is obvious that AD and KS are extremely sensitive to the disruptive effects of events occurring during the delay period, and this may be the critical factor in determining whether an apparently greater rate of forgetting is observed. Disruption to

performance from events which occur following the initial stimulus presentation (but prior to recall or recognition) has been termed 'retroactive' interference. However, KS and AD subjects also show a high degree of susceptibility to the disruptive effects of events which occur prior to presentation of the to-be-remembered stimulus (i.e. 'proactive' interference). For instance, AD and KS subjects show a tendency to perseverate on previously emitted responses when recalling words (Butters, 1985; Butters et al., 1987), in recognition of pictures (Butters, et al., 1983) or when recalling stories (Butters et al., 1987). Also, Delis et al. (1991) conducted a comparison of AD and KS subjects for performance on the California Verbal Learning Test, part of which involves the learning of two lists of words. They found that AD and KS subjects performed similarly on all indices, including ability to learn a list, number of words recalled immediately and after a delay, ability to utilise a cue to aid recall and recognition performance. Furthermore, both AD and KS subjects demonstrated a susceptibility to proactive interference, in that when asked to recall the second list learnt, there was a high rate of intrusions from the first list learnt. Kramer et al. (1988) extended this finding by demonstrating that the number of these intrusions was significantly increased by imposing a longer delay between list presentation and recall trials.

In conclusion, AD and KS subjects display a number of similarities in their memory impairments. Although it is difficult to compare the level of memory deficit in AD with the level of deficit in KS, because so few studies have made direct comparisons, both disorders result in similar disruptions. These similarities include: a disruption to the primacy effect when presented with a list of items to remember; an impairment in DMTS (either in terms of a greater rate of forgetting or a delay-independent reduction in performance); and in general, a greater susceptibility to the disruptive effects of extraneous events on current memory performance. Studies which have compared AD and KS subjects with the same procedure (e.g. Kopelman, 1985, 1991) indicate that although the deficits may be similar, there is a greater degree of disruption observed in the AD group. Comparative studies of neurological disorders with different etiologies is

an area which has only recently has received attention. However, there are many indications that the degree of similarity observed between KS and AD may not be shared with other well-known disorders, such as Parkinson's Disease (e.g. Sullivan & Sagar, 1989; Kramer, Levin, Brandt & Delis, 1989) or Huntington's Disease (e.g. Moss, Albert, Butters & Payne, 1986; Delis et al., 1991; Butters, Tarlow, Cermak & Sak, 1976; Butters et al., 1985; Beatty et al., 1988). Given that there exists a similarity between AD and KS in terms of similar memory disruptions, albeit to different degrees, it is of value to examine whether there are any similarities in terms of the observed neuropathology. Indeed, a review of the research below (Section 1.1.2) indicates that both disorders display neuropathology in the basal forebrain (which includes the medial septum and nucleus basalis regions) with a consequent disruption to the supply of the neurotransmitter acetylcholine to various hippocampal and cortical regions.

1.1.2 Neuropathology in Alzheimer's Disease and Korsakoff's Syndrome

A number of investigations have been made of the neurological changes that take place in AD and KS brains. These studies provide some indication of the brain regions that may be involved in the memory deficits observed in these two disorders. The following discussion is a brief overview of some of the major changes in gross anatomical brain regions and neurochemical pathways that have been implicated in the memory disruptions observed in AD and KS.

In AD there is a wide range of neuropathology exhibited. For instance, several neurochemical pathways show a disruption of function, including the cholinergic (Perry et al., 1978), noradrenergic (Zornetzer, 1986) and serotonergic (Altman & Normile, 1986) pathways. A noradrenergic deficit has been shown in a number of studies with reduced levels of noradrenaline (e.g. Adolfsson, Gottfries, Roos & Winblad, 1979) and dopamine B-hydroxylase (Perry et al., 1981). The major source of noradrenaline in the brain is the locus coeruleus, and a number of studies have reported a loss of cells (e.g. Mann, Yates & Marcyniuk, 1984; Tomlinson, Irving & Blessed, 1981) and the presence of neurofibrillary tangles (Ishii, 1966) in this region. However, the role of noradrenergic

depletion in the symptoms observed in AD is equivocal. Some studies have reported that no correlation exists between reduction in locus coeruleus neurons, noradrenaline levels in the temporal cortex and clinical symptoms (e.g. Perry et al., 1981), but other studies have reported significant correlations when noradrenaline levels in the hypothalamus are used (e.g. Adolfsson et al., 1979). With regard to the serotonergic system, loss of serotonin innervation in AD brains has been demonstrated using measures of serotonin, hydroxyindole acetic acid concentrations and imipramine binding (Adolfsson et al., 1979; Bowen, et al., 1983). These biochemical observations of serotonergic function correlate with reports of reduced cell counts in the raphe nuclei (Bowen et al., 1983). However, the role of serotonin disruption in AD is also questionable. Bowen et al. (1983) only observed a reduction in serotonin levels for younger 'pre-senile' dementing subjects and not for older subjects. Other neurochemicals which show indications of disruption in AD are somatostatin (Davies, 1986), GABA in the cortex and hippocampus (Reisen et al., 1980) and cortical peptides such as neurotensin, substance P and thyrotropin-releasing hormone (see Rossor & Iversen, 1986). As well, a number of other brain regions exhibit primary cell damage that may be important in the symptoms of AD (e.g. the subiculum and entorhinal cortex - Heyman, Van Hoesen, Darnasic & Barnes, 1985). Thus, a number of brain regions and neurochemicals may be implicated in the behavioral symptoms of AD.

Among the variety of neuropathological aspects in AD, one neurochemical system has received intense interest over the past 15 years - the cholinergic system. A substantial body of research has confirmed that decreases in the activity of choline acetyltransferase (ChAT - a specific cholinergic marker) and acetylcholinesterase (AChE - an enzyme responsible for the breakdown of the neurotransmitter acetylcholine) in the cortex and hippocampus are among the most consistent and severe abnormalities found in AD (e.g. Davies & Mahoney, 1976; Bowen, Smith, White & Davison, 1976; Perry et al., 1978). A large proportion of the cholinergic system is composed of several major pathways, originating in the basal forebrain (Fibiger, 1982). The major source of cholinergic projections to the cerebral cortex is a group of basal

forebrain cells lying adjacent to the globus pallidus, called the nucleus basalis of meynert. In contrast, the cholinergic innervation of the hippocampal formation originates from the medial septal nucleus and the vertical limb of the diagonal band. As with biochemical studies of cholinergic activity markers, there is extensive research demonstrating significant cellular changes in these basal forebrain structures for AD sufferers (e.g. Vogels et al., 1990).

Of the various basal forebrain regions investigated in AD subjects, the nucleus basalis has received the most attention, with a number of studies reporting a loss of cells in this region along with a concurrent loss of acetylcholine activity markers in the cortex (Whitehouse et al., 1980; Tagliavini & Pilleri, 1983; Candy et al., 1983). Extensive evidence also exists that demonstrates cell loss and shrinkage of the cholinergic neurons in the medial septal region, with a concurrent loss of acetylcholine activity in the hippocampal formation (Nikano & Hirano, 1982; Mesulam, Mufson, Levey & Wainer, 1983; Gertz, Cervos-Navarro & Ewald, 1987; Arendt, Bigil, Arendt & Tennstedt, 1983). An important finding has been the demonstration of significant correlations between current ChAT activity and a mental test score or severity of dementia in AD subjects (Perry et al., 1978; Doucette, Fisman, Hachinski & Mersky, 1986). Therefore, disruption to cholinergic activity, presumably through cellular damage in various basal forebrain regions, has been implicated in the memory disruptions observed in AD.

With regard to KS, the three subcortical brain regions which have been implicated in the memory deficits observed in KS are the dorsomedial thalamus, mammillary bodies and the basal forebrain. Victor, Adams & Collins (1971) examined the brains of a large sample of KS sufferers and found that in 38 out of 43 brains there was extensive atrophy of the dorsomedial nucleus of the thalamus. In the 5 cases without atrophy to the thalamus, but with damage to the mammillary bodies, there were no symptoms of a memory disorder. Therefore, the findings of Victor et al. (1971) indicate that either the dorsomedial thalamic lesions, or the combination of dorsomedial and

mammillary lesions is critical to the memory disruptions exhibited in KS. However, more recent research has employed more sensitive tests of memory than originally conducted by Victor et al., suggests that the mammillary rather than dorsomedial lesions may be critical. Mair et al, (1979) examined, in depth, the memory deficits of two subjects diagnosed with KS and observed a number of deficits consistent with the syndrome (see Section 1.1.1). Mair et al. (1979) did not find much evidence of neuropathology in the dorsomedial thalamus, although there was a thin band of gliosis lying anterior to the medial dorsal nucleus. Rather they noted that there was marked gliosis, shrinkage and discoloration in the medial nuclei of the mammillary bodies. These observations have been replicated in a more recent study by Mayes, Meudell, Mann & Pickering (1988) with two more KS subjects. Therefore, although an important role may be played by mammillary body damage in the memory deficits seen in KS, the human data to date do not provide an answer as to whether damage in the mammillary bodies alone is sufficient to cause the psychopathology observed.

The basal forebrain is a third region which has only more recently been implicated in KS. Arendt et al. (1983) demonstrated that in both AD and KS there is a selective loss of the cholinergic neurons in the nucleus basalis and medial septal regions of the basal forebrain, and that this loss is not observed in many other neurodegenerative diseases such as Huntington's or nondementing Parkinson's disease. As would be expected of cell damage in these regions, Antuono et al. (1980) found that throughout both the neocortex and hippocampus there is a significant reduction in ChAT activity for both AD and KS subjects. In both the Arendt et al. (1983) and Antuono et al. (1980) studies, the degree of cellular loss and reduction in ChAT were greater in the AD brains than in KS brains. However, although the study of Arendt et al. (1983) implicates both the nucleus basalis and medial septal regions in KS, Mayes et al. (1988) examined the nucleus basalis and septal region in their two KS subjects and found no reduction in nucleolar volume in the nucleus basalis, although there was a reduction in the nucleolar volume in the septal region.

In summary, a review of the relevant research reveals that damage in the basal forebrain is a key aspect of the neuropathology in AD & KS and may be responsible for some of the memory deficits observed in both disorders. That is, the overlap in neuropathology between AD and KS may result in some, or all, of the observed overlaps in memory disruption. Either the nucleus basalis (perhaps via a cholinergic projection to the cortex) or the medial septum (perhaps via a cholinergic input to the hippocampal formation) may be critical regions, although the study of Mayes et al. (1988) tends to more strongly implicate the medial septum ('MS') in memory function. With respect to KS, in addition to basal forbrain regions the mammillary bodies ('MB') are also of interest, since there is evidence that damage in this region may be involved in the observed memory disruptions.

Aside from both being implicated in the memory impairments of AD and/or KS, the MS, MB are anatomically related in that along with various other brain structures including the hippocampal formation ('HF') they comprise some of the interconnected components of the limbic system (Swanson, 1982, 1984). The MS shares a functional relationship with the HF in that it is a major source of hippocampal acetylcholine, supplied via fimbria-fornix projections, and likewise receives input from the HF via the lateral septum (Swanson, 1982, 1984). The MB receive input from the MS and HF, and in turn project back to the subicular complex portion of the hippocampal formation with projections originating in the medial mammillary nuclei and running via the anterior thalamus; as well as more directly via histaminergically active pathways arising in the supra mammillary region and projecting to the dentate gyrus region of the hippocampal formation (Swanson, 1982, 1984; Ino et al., 1988; Wyss, Swanson & Cowan, 1979; Segal, 1979; Barbin et al., 1976; Haas et al., 1978). Thus, apart from the MS and MB having potential roles in memory, they are related in terms of the functional anatomical connections they share with each other and the HF. Figure 1.4 shows the various major anatomical relationships between the HF, MS and MB.

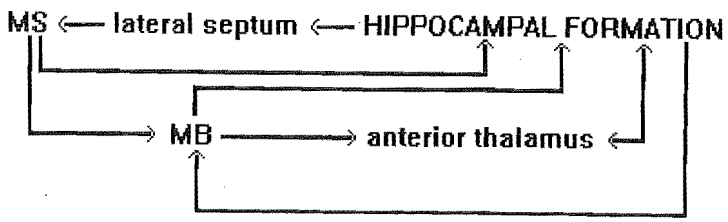

FIG 1.4 Some major interconnections between the hippocampal formation, medial septum and mammillary bodies in the mammalian brain (based on Swanson, 1982, 1984; Wyss et al., 1979; Segal, 1979; Ino et al., 1988). The medial septum (MS) projects to both the medial and supra mammillary nuclei within the mammillary body region (MB) and to all fields of the hippocampal formation (i.e. dentate gyrus, Ammons Horn, subicular complex and Entorhinal cortex). The supramammillary region projects to the dentate gyrus of the hippocampal formation, whilst the medial mammillary region projects to the hippocampal formation via the anterior thalamus and presubiculum. The hippocampal formation projects to the MS via the lateral septum as well as to the medial and supra mammillary regions.

Unlike the case for KS, the MB have not been implicated in AD. Therefore, an investigation and comparison of the roles played by the MS and MB is of interest in determining not only whether damage to one or either of the regions results in memory impairments similar to those observed in AD and KS but also in providing clues as to the functional importance and equivalence of these two hippocampal connections. Unfortunately, establishing with any certainty the roles played by distinct brain regions is problematic if one relies on human neuropathological studies alone, because AD and KS subjects exhibit wide and sometimes idiosyncratic neuropathologies. Related to this, most AD subjects die in the advanced stages of their disease and few of the more mild cases come to autopsy. Furthermore, because of the difficulty involved in conducting such a study, few researchers have provided both detailed behavioral and neuropathological profiles from case studies.

The problem of establishing causality between brain regions and memory function can be overcome by conducting experimental studies. Obviously, most surgical and pharmacological studies have employed animals (typically the rat) as subjects, although there is a body of relevant research which has examined human memory performance under the influence of cholinergically-active drugs. The following sections (1.2 and 1.3) will examine the relevant human and nonhuman experimental research which indicates, as does the human clinical data, that the MS and MB may play key roles in normal memory function.

1.2 CHOLINERGIC DISRUPTION AND MEMORY

In addition to the indications from the clinical data described above, experimental research with humans and nonhumans has indicated that disruptions to central nervous system (CNS) cholinergic activity may be responsible in part for the memory impairments in AD and KS. The CNS cholinergic system comprises two main components - the nucleus basalis projection to the cortex and the MS projection to the HF. As will be discussed in Section 1.2.1, pharmacological investigations with anticholinergic drugs have revealed similar memory impairments to those observed in AD and KS. Thus, these pharmacological studies implicate both the MS and/or nucleus basalis areas in memory function but unfortunately lack the specificity to determine their respective roles. A brief review of the effect of nucleus basalis lesions on memory is given in Section 1.2.2. This section concludes that although there is evidence for a role of this region in memory function, the results of some studies have been equivocal, particularly when lesions which are relatively more specific to the nucleus basalis - cortex cholinergic projection have been used. Section 1.2.3 reviews some of the evidence relating to MS lesion effects on memory-task performance. This section concludes that there is considerable support for a role of the MS region in memory function, thus supporting the potential value of exploring the effects of lesions to this region in greater detail. Finally, Section 1.2.4 discusses the need to examine MS lesion

effects in combination with other structures implicated in memory function and which are connected to the HF but which do not constitute part of the cholinergic input to it (in particular the MB).

1.2.1 Effects of Anticholinergic Drugs on Memory

A great deal of support for the importance of brain structures involved in CNS cholinergic activity on memory performance has come from human and animal research investigating the effects of CNS cholinergic disruption via pharmacological means. The human pharmacological evidence stems from the fact that blocking CNS cholinergic mechanisms with scopolamine induces memory impairments in tasks which also reveal an impairment in both AD and KS subjects. For example, Crow & Grove-White (1973) and Frith et al. (1984) have demonstrated that administration of scopolamine to young subjects results in an impairment for recall of list items at the beginning of a list but not at the end. That is, as observed in AD and KS, there is a loss of the primacy effect but not of the recency effect. Also, Caine et al. (1981) showed that subjects who receive scopolamine are impaired on the Brown-Peterson recall task. A recent study by Kopelman & Corn (1988) investigated human memory performance under the influence of scopolamine on a variety of memory tasks used in demonstrating a similarity between AD and KS subjects. They found that a .4 mg dose of scopolamine induced impairment on recall of a sequence of corsi blocks in a manner that was analogous to the pattern observed in AD and KS using the same task (Kopelman, 1991). That is, at a delay of 0 s, recall is unimpaired; at the shortest delay interval performance is worse in the scopolamine group compared to controls, but at longer subsequent intervals the difference between groups remains constant even though performance in both groups declines with increases in delay. Kopelman & Corn (1988) also demonstrated similar impairments in memory using the Brown-Peterson verbal recall task following administration of scopolamine. However, the effect of cholinergic blockade was perhaps more similar to the deficits shown by KS subjects than AD subjects in that although cholinergic blockade impaired performance the effect was not as severe as observed in AD.

It may be that higher doses of scopolamine results in even greater memory impairments than observed by Kopelman & Corn (1988) if the degree of memory impairment is directly related to the degree of cholinergic blockade. It is interesting to note that AD subjects show a greater degree of ChAT depletion in the HF but not the neocortex compared to KS subjects (Antuono, 1980), so the key pathway in determining how disruptive cholinergic depletion is on memory may be the cholinergic input from the MS to the HF. Support for the importance of hippocampal acetylcholine activity comes from the observation that the HF shows greater ChAT depletion than the neocortex in AD subjects (Antuono et al., 1980; Perry, 1986). However, these findings need to be replicated across a greater number of studies since the extent of ChAT disruption observed varies a great deal within and across studies which have investigated AD.

As with humans, a variety of nonhuman species display alterations in memory task performance when administered CNS-active cholinergic drugs such as scopolamine and atropine. The vast majority of non-human pharmacological research has been conducted using rats. A number of studies have demonstrated that rats are impaired in the standard 8-arm radial maze task described by Olton & Samuelson (1976) (e.g. Levin, Rose, McGurk & Butcher, 1990; Beatty & Bierley, 1986; Watts, Stevens & Robinson, 1981). In the radial maze task, each arm is baited with food and a rat is free to visit each arm. An error is a return to an already visited arm on that trial. Control rats learn this task very quickly and display few errors; however anticholinergics impair both acquisition and performance in this task. Other traditional memory tasks used with rats also show disruption with anticholinergics, including T-maze arm alternation (e.g. Beninger, Jhamandas, Boegman, El-Defrawy, 1986) and the Morris Water Maze (e.g. Paylor & Rudy, 1990). Thus, it appears that anticholinergics disrupt both human and nonhuman memory performance.

Of particular interest in the synthesis of human and nonhuman research are those nonhuman studies which have used memory tasks analogous to those often used with

human subjects (e.g. the list-item memory tasks or the DMTS tasks described above and in Section 1.1.1). To a large extent such research has been less common than studies which have made use of more traditional memory tasks such as the radial-arm maze and Morris Water Maze tasks. For example, animal research has not investigated the effect of anticholinergic drugs on the primacy and recency effects in memory for list items. This may be because of the difficulty in demonstrating these effects in animals (see Section 1.3.1 for a description of the methods used to assess memory for list items in animals) and the large number of training sessions, and hence drug administrations, required in procedures used to investigate memory for list items in animals. There are, however, several studies which have examined the effects of anticholinergic drugs on rat performance over a range of delays in versions of DMTS.

A review of the relevant DMTS studies indicates that similar memory impairments may occur in rats as those observed in humans following anticholinergic drug administration. For example, Spencer, Pontecorvo & Heise (1985) trained rats on a relative of DMTS called continuous non-matching-to-sample, and investigated the effects of scopolamine. They presented rats with either a bright or dim light which was then switched off during the interstimulus delay (which varied between 2.5 and 10 s). At the end of the delay, either the same (incorrect) light stimulus was turned on, or a different (correct) light stimulus was turned on. To gain access to food reinforcement the rats task was to press a lever if the stimulus was different from the one that immediately preceded it. A bar press when the current stimulus was the same as the preceding one did not provide access to food. Spencer et al. (1985) found that as the dose of scopolamine increased, accuracy was decreased by an equal amount at each delay. However, a danger of this procedure is that accuracy may reduce as a function of 'poorer memory' across delays or as a function of increases in the level of overall responding since the rat can collect all the available reinforcers simply by responding on each trial. That is, simply by responding on each trial all the available reinforcers in the session can be collected. Whether this was the case in Spencer et al. (1985) is unknown as they did not report data showing response rates as a function of delay or

drug group. Irrespective of these concerns, the lack of a delay-dependent memory deficit following scopolamine administration in rats has been demonstrated over a wide range of doses in three other studies which used DMTS tasks for lever position in an operant chamber (Dawson et al., 1991; Dunnett, 1985) and auditory stimuli with bias-free measures of accuracy (Kirk, White & McNaughton, 1988). These studies have demonstrated that accuracy is equally disrupted at each delay in animals which have received scopolamine, a pattern which is the same as observed in KS and AD subjects relative to controls when the 0 s delay is not included in analysis of the rate of forgetting (see Figures 1.2 and 1.3 in Section 1.1.1). Therefore, CNS acetylcholine activity appears to be important in normal memory function and may, to some degree, underlie the memory deficits observed in AD and KS.

Although the nonhuman and human pharmacological studies described above are a source of support for the central role of acetylcholine activity in memory, this research lacks the specificity to tell us about brain region function, and hence does not reveal much about the role of the MS - hippocampal connection or whether it plays a role in memory that is dissociable from the nucleus basalis - neocortex connection. Yet both the MS and nucleus basalis regions are aspects of the neuropathology in AD and KS, so it is important to examine their relative contributions to memory function. The value of brain lesion studies is that they can be used to disrupt neuroanatomical pathways selectively and hence allow a specific examination of the role of various brain regions in memory. The rationale of lesion studies is that by disrupting specific aspects of memory function clues are provided as to the role of an intact brain region and whether this brain region has any implications for the memory disruptions observed in human neurological disorders. The next two sections (1.2.2 and 1.2.3) describe research that has examined the effects of nucleus basalis lesions and MS lesions on memory performance in rats.

1.2.2 The Effect of Nucleus Basalis Lesions on Memory

The nucleus basalis magnocellularis (NBM) in the rat is a group of cells located in the ventromedial region of the globus pallidus which supplies the majority of cholinergic input to the cortex and is thought to be homologous to the nucleus basalis of meynert in humans. A number of rat-lesion studies have suggested an important role for the NBM in memory. For example, Beninger et al. (1986) gave rats a neurotoxic lesion of the NBM and ran them in a modified version of the standard radial maze task. In this procedure, a certain set of arms are always baited at the beginning of a trial and the other arms remain unbaited. A measure of the 'shorter-term' aspects of memory is obtained by counting the number of visits to baited arms versus re-visits to these previously baited arms during the trial. A measure of the 'longer-term' or 'procedural' aspects of memory is obtained by counting visits to baited arms versus visits to arms that are never baited. Beninger et al. (1986) found that the greatest memory impairment was to their measure of working memory performance. Apart from displaying deficits in the radial maze task, rats with NBM damage have been shown to have memory impairments in other procedures. For example, when rats are given a neurotoxic lesion of the NBM with Ibotenic acid, disruptions occur to performance in: T-maze stem alternation (e.g. Salamone, Beart, Alpert & Iverson, 1984; Hepler, Olton, Wenk & Coyle, 1985a); T-maze win-stay and lose-shift procedures (e.g. Hepler et al., 1985b); and in the Morris Water Maze (e.g. Sweeney, Hohmann, Moran & Coyle, 1988; Riekkinen, Sirvio & Riekkinen, 1990).

Despite the evidence suggesting a role of the NBM in memory there exist a number of inconsistencies observed in the effect on memory following NBM lesions (see Dekker, Conor & Thal, 1991). For instance, some studies have not found an impairment in radial-arm maze performance (e.g. Fibiger, Murray & Phillips, 1983; Kesner, DiMattia & Crutcher, 1987) or an impairment in the Morris Water Maze task (e.g. Hagan et al., 1988). In other tasks, more akin to the human-memory tasks described in Section 1.1.1, NBM lesions have failed to result in memory deficits. For example, Kesner (1988b) noted that when rats are presented with a list of arms to

remember in a radial maze serial-probe recognition task ('SPR') and are given a NBM lesion, they show no impairment in subsequent ability to recognise list arms (this task is discussed in further detail in Section 1.3.1). Also, Dunnett, Rogers & Jones (1989) examined the effect of NBM lesions on DMTS performance and failed to observe an impairment in performance either in terms of an increase in the rate of forgetting or a delay-independent reduction in accuracy. So, although current research suggests that NBM damage may result in an impairment in some memory tasks, findings are inconsistent across studies which have used memory tasks that are analogous to those used to investigate human memory.

The inconsistencies observed between NBM-lesion studies may be partly the result of the heterogeneous nature of the NBM region. Most studies have used neurotoxic lesions (e.g. Kainic, Ibotenic or Quisqualic acid) which all have the advantage of being relatively more selective in their damage to neuronal perikarya in the NBM as opposed to damaging the fibres of passage originating in other brain regions. However, the degree of selectivity depends on the neurotoxin used and the dosage (see Dunnett, Whishaw, Jones & Bunch, 1987). A number of researchers have now compared the effect on memory of various neurotoxins and concluded that toxins that are more specific to cholinergic neurons in the NBM (e.g. Quisqualic acid) result in little or no memory disruptions compared to less specific neurotoxins (e.g. Kainic or Ibotenic acid). For example, Markowska, Wenk & Olton (1990) found that both Ibotenic and Quisqualic acid lesions resulted in an impairment in the acquisition of a DNMTS task and in a spatial DMTS task. Ibotenic lesions produced a 45 percent reduction in cortical ChAT compared to Quisqualic lesions which produced a 74 percent reduction in cortical ChAT. However, rats with a Quisqualic lesion displayed less of a deficit in task acquisition and unimpaired subsequent retention of performance compared to rats with an Ibotenic lesion. Greater behavioral impairments, but smaller ChAT reductions, when using Quisqualic versus Ibotenic acids have also been observed in a T-maze alternation task (Wenk, Markowska & Olton, 1989) and choice accuracy in a selective

attention task (Robbins et al., 1989). Therefore, impairments, when they do occur, do not seem to rely solely upon a disruption to cortical cholinergic activity.

We know from the pharmacological evidence presented in Section 1.2.1 that cholinergic disruption in the CNS produces memory impairments. However, for the reasons given above, it is not possible to interpret the results of AD and KS memory impairments or the results of the relevant pharmacological studies solely in terms of disruption to the NBM - cortex cholinergic projections. A major alternative to the NBM - cortex projection is the MS - hippocampal pathway, which is another cholinergic pathway in the CNS and also an aspect of the neuropathology of AD and KS. Hence, a potentially profitable avenue for investigation is the role of the MS in memory function. It may be for example that damage in the MS region, which disrupts cholinergic activity in the HF, will result in memory impairments similar to those observed in AD, KS and under the influence of anticholinergic drugs. Section 1.2.3 reviews the relevant literature which has supported the conclusion that MS lesions do indeed result in an impairment to memory function.

1.2.3 The Effects of Medial Septum Lesions on Memory

MS Lesion Effects in Rats

A number of rat-lesion studies have shown that damage in the MS results in an impairment to memory. As mentioned in Section 1.1.2, the MS shares a functional relationship with the HF in that it is a major source of hippocampal acetylcholine, supplied via fimbria-fornix projections, and likewise receives input from the HF via the lateral septum (Swanson, 1982, 1984). At a behavioral level, there is a great deal of direct support for the conclusion that the MS region plays an important role in memory. For example, rats with MS damage show impairments in T-maze alternation (e.g. Rawlins & Olton, 1982; Givens & Olton, 1990) and the radial maze SPR task for a list of arms (Kesner, Crutcher & Beers, 1988; Kesner & Adelstein, 1989). The T-maze alternation task and SPR tasks require the rat to remember where it 'last was' in a trial (i.e. match or nonmatch-to-sample), in order to gain food. Therefore there is evidence

that MS-lesioned rats perform poorly in tasks which require memory for short-term trial-dependent information (or 'working memory' as operationally defined in nonhumans).

The evidence for MS damage causing disruption to memory for the longer-term, trial-independent aspects of memory (or 'reference memory' as operationally defined in nonhumans) is equivocal in studies using the Morris Water Maze. Although some recent studies have questioned the reliability of observing deficits in the Morris Water Maze task following MS damage (see Barone et al., 1991; Decker, Radek & Pellymounter, 1990; Decker, Radek, Majchrzak & Anderson, 1992) a number of studies have found performance deficits in this task (e.g. Miyamoto, Kato, Narumi & Nagaoka, 1987; Hagan et al., 1988). The reasons for this discrepancy in the effects of MS damage on the Water Maze task are not clear. Barone et al. (1991) suggested that studies which had shown a deficit may have done so via nonspecific damage to other brain regions (e.g. fimbria-fornix). Indeed when Barone et al. (1991) caused relatively specific damage to the MS region by infusing colchicine directly into it, no impairment in the Morris Water Maze task was observed. However, this explanation does not account for the finding of Decker et al. (1992) who found no effect of either relatively less specific damage caused by radiofrequency, or relatively more specific damage caused by Quisqualic acid, on the Water Maze task.

Further evidence of significant and lasting working memory deficits, and more convincing evidence of reference memory deficits following MS damage, come from the many studies which have used the 8-arm radial-maze task (e.g. Hepler et al., 1985b; Harrell, Barlow & Parsons, 1987; Harrell, Barlow & Davis, 1983; Crutcher, Kesner & Novak, 1983; Miyamoto et al., 1987; Olton, Walker & Gage, 1978; Decker et al., 1992). Both Harrell et al. (1987) and Arendt et al. (1989) have used the modified version of the 8-arm maze task, described earlier, to assess reference vs working memory disruptions. Both studies found an impairment in both the trial-dependent working memory and trial-independent reference memory. That is rats returned to previously baited arms in a trial and visited arms that were never baited in any trial. Arendt et al's

(1989) study also demonstrated an impairment in both working and reference memory even when spatial location or non-spatial, visual / tactile cues were used to signal correct arms. These results, as with the T-maze, SPR research, and much of the Morris Water Maze research, suggest that MS lesions result in memory impairments for long-term invariant information as well as memory for variable events in the short-term.

The Effect of Medial Septal Damage on Hippocampal Acetylcholine Activity

There are several lines of evidence which support the idea that MS damage impairs memory via the resultant disruption to HF cholinergic activity. Firstly, the evidence reviewed in Section 1.2.1 indicated there is substantial evidence that anticholinergic drugs cause alterations in human and nonhuman memory performance on a variety of tasks. Furthermore, these alterations are similar to the memory impairments observed in neurodegenerative disorders such as AD and KS which exhibit neouropathology in basal forebrain (MS and NBM) cholinergic brain regions. Second, several studies have demonstrated that the greater the degree of MS damage, the greater the degree of cholinergic disruption in the HF and the greater the level of memory-task impairment. For example, such concurrent patterns of disruption have been observed in studies using a spatial-discrimination version of the Morris Water Maze, a SPR task in an 8-arm maze and in a T-maze alternation task (e.g. Decker et al., 1992; Kesner et al., 1988; Kesner & Adelstein, 1989; Givens & Olton, 1990).

Finally, the potential disruption to memory resulting from a disruption in hippocampal function via reductions in cholinergic activity is an idea which is consistent with the considerable amount of literature indicating that the HF itself plays a critical role in memory (for reviews see O'Keefe & Nadel, 1978; Olton, Becker & Handelmann, 1979; Gray, 1982; Gray & McNaughton, 1983; Rawlins, 1985; Squire, 1992). For example, performance in Morris Water Maze and various 8-arm maze tasks are disrupted in rats with hippocampal damage (e.g. Morris, Garrud, Rawlins & O'Keefe, 1982; Morris, Hagan & Rawlins, 1986; Kesner & Novak, 1982; Kesner et al., 1988; Kesner & Adelstein, 1989). Similarly, in spatial and nonspatial DMTS and DNMTS

tasks, rats with bilateral lesions of the HF show slower acquisition than controls (Peinado-Manzano, 1990; Jagielo, Nonneman, Isaac & Jackson-Smith, 1990). Finally, it is widely recognised that humans with bilateral hippocampal damage display severe amnesia and disruptions in a variety of memory tasks (e.g. Milner, 1978).

However, despite the evidence supporting the role of the HF in memory there are several discrepancies in the literature. For example, a number of studies have found that recognition memory for nonspatial objects is not impaired following HF damage (Aggleton, Hunt & Rawlins, 1986; Rothblat & Kromer, 1991; Mumby, Wood & Pinel, 1992; Morris et al., 1986). Morris et al. (1986) conducted an experiment using the Morris Water Maze in which rats were trained to swim to either a non-visible fixed platform that was spatially constant over trials or swim to a visible platform that was constant over trials. They found that rats with hippocampal lesions learnt the nonspatial task as quickly as controls but that they were unable to learn the spatial version. Consequently, there is a great deal of debate in the literature regarding the degree of memory impairment in rats with HF lesions when using nonspatial stimuli (Morris et al., 1986; Squire, 1992; Rasmussen, Barnes & McNaughton, 1989). Thus, although there is already support for the role of the HF itself in memory function the precise nature and extent of this role is still a major topic of investigation.

One avenue of investigation that may help clarify the role of the HF is the investigation of the behavioral functions played by brain structures connected to it. In particular since the MS provides an input to the HF and has also been implicated in memory, damage to the MS itself provides a relatively discrete and specific means to disrupt normal hippocampal function. Furthermore, since the MS is also a major part of the cholinergic input to the HF, the assessment of MS-lesion effects may yield an integration of the hippocampal studies with the pharmacological data. Therefore, further investigation of the MS will not only clarify its role in memory but may also help to clarify the role of the HF.

1.2.4 The Medial Septum Versus Other Hippocampal Connections

The Effects of Fimbria-Fornix Lesions

In addition to examining the effects of MS lesions on memory performance, the investigation of lesion effects to other structures connected to the HF, and which are also implicated in memory function, is likely to be worthwhile. For instance, an additional (albeit indirect) line of support for role of the MS in memory comes from studies which have shown fimbria-fornix lesions to be effective in disrupting memory. Lesions to the fimbria-fornix disconnect the MS input to the HF, rather than causing direct damage to either structure in particular. Not surprisingly, a number of studies have shown that fimbria-fornix lesions result in a severe reduction to hippocampal acetylcholine markers and often produce severe memory impairments (e.g. in memory for nonspatial stimuli in a 4-arm maze - Olton & Feustle, 1981; working and reference memory in a 17-arm maze - Olton et al., 1979; the Morris Water Maze - Sutherland & Rodriguez, 1989; T-maze alternation - Rawlins & Olton, 1982; 8-arm maze task - Jarrard, Okaichi, Steward & Goldschmidt, 1984; and in an automated DMTS task Dunnett, 1985; Aggleton, Keith & Sahgal, 1991). However, it is important to note that fimbria-fornix lesions also disconnect brain regions other the MS from the HF (e.g. the MB) and that relatively more specific lesions to these structures can show dissociable effects on memory. For example, Tonkiss, Feldon & Rawlins (1990) explored the effects of discrete lesions to the descending columns of fornix by comparing the effects of transections of the subicular input to the lateral septum versus the subicular input to the MB and anterior thalamic nuclei. They found that disconnection of the MB/anterior thalamus input produced delay-dependent impairments in T-maze rewarded-alternation performance, but that disconnection of the input to the lateral septum input did not. The disconnection of multiple areas may underly the reason why fimbria-fornix lesions often result in more severe memory impairments than MS lesions alone (e.g. Sutherland & Rodriguez, 1989), or even sometimes lesions directly to regions within the HF (e.g. Jarrard et al., 1984). These results are not particularly surprising given the indications from the human neuropathological data that brain regions other than the MS are also implicated in the memory disruptions of AD and KS. Therefore, a number of

brain regions connected to the hippocampus and/or MS may also play important roles in memory function. Thus, it is important when assessing the effects of MS damage on memory to do so in conjunction with an assessment of other brain regions which - 1. share an anatomical relationship with the MS; and 2. display evidence that they too may be involved in memory. As indicated in the human neuropathological discussion of AD and KS in Section 1.1.2, one such area is the MB. Hence, as was done with the relevant MS-lesion studies, it is worthwhile reviewing the research which has examined the effects of MB lesions on memory.

The Effect of Mammillary Body Lesions on Memory

As with the MS, there is support from rat lesion studies for the possibility that the MB is a brain region which plays a critical role in memory. To recap, the MB are a component of the limbic system which serve as a target structure from projections from both the HF (via the postcommissural fornix) and the MS. Furthermore, the supra mammillary region of the MB projects back directly to the dentate gyrus of the HF, whilst the medial mammillary region projects indirectly back to the presubiculum region of the HF via the anterior thalamus (Swanson, 1982,1984; Allen & Hopkins, 1989; Ino et al., 1988; Segal, 1979; Wyss et al., 1979). Lesions of the MB produce impairments in spontaneous and rewarded alternation, as indicated by erroneous returns to a T-maze arm visited on the preceding trial (Field, Rosenstock, King & Greene, 1978). These perseveration errors by the MB rats increase by a greater proportion than seen in control rats as the delay between trials is increased (Rosenstock, Field & Greene, 1977; Beracochea & Jaffard, 1987). Furthermore, MB lesions also produce an impairment in post-operative acquisition of the Morris Water Maze task that is similar to that observed by MS lesioned rats (Sutherland & Rodriguez, 1989).

Despite some studies supporting the role of the MB region in memory function, there are a number of studies which have failed to find an impairment following damage in this region. Whereas research on the MS (like the HF) has often focused on working versus reference memory and spatial versus nonspatial memory, there have been

comparatively few studies which have addressed these distinctions with respect to the role of the MB. However, existing research suggests that unlike MS-lesioned rats, MB-lesioned rats do not appear to exhibit working and reference memory impairments in the radial maze task using non-spatial (visual plus tactile) stimuli. For example, Jarrard et al. (1984) found that rats with MB lesions did not exhibit an increase in errors in terms of returning to a previously baited arm on a given trial or in terms of visiting an arm that was never baited on any trial. With spatial stimuli the results of the radial maze task are mixed. The study by Jarrard et al. (1984) also examined performance in the same apparatus but instead with the spatial location of an arm as the stimulus. This procedure also revealed no impairment in either the working or reference memory components of memory. However, Saravis, Sziklas & Petrides (1990) used the standard 8-arm maze procedure in which all 8 arms are baited at the beginning of a trial. They found that for MB-lesioned rats there was a large and significant number of errors made in terms of returning to previously chosen arms on a trial. Equally inconclusive are the various studies which have used variations of the DNMTS procedure. For example, Saravis et al. (1990) found that rats in an 8-arm maze DNMTS task showed a delay-independent impairment in performance following MB damage. Whereas Aggleton, Hunt & Shaw (1990) and Aggleton et al. (1991) respectively failed to observe an impairment in Y-maze and operant-based DNMTS procedures following MB damage (these experiments are discussed in greater detail in Section 1.3.2). Thus the evidence for the role of the MB region in memory remains relatively equivocal and more research needs to be conducted.

In conclusion, rat-lesion studies have indicated that both the MS and MB regions of the rat brain may play a role in memory function, as revealed by disruptive effects of lesions to these regions on performance in a number of memory tasks. However some of the existing data, to small degree with MS and a greater degree with MB, are equivocal and more research needs to be conducted in order to determine their respective role(s) in normal memory function. Thus, the focus of the present research was on these two brain structures.

1.3 THE COMPARISON OF MEDIAL SEPTUM AND MAMMILLARY BODY LESION EFFECTS

To recap the major points of Sections 1.1 and 1.2, the human neuropsychological and neuropathological data as well as pharmacological data has implicated the basal forebrain region as important in memory function. Consequently, the MS (which is located in the basal forebrain) is an obvious area to investigate with respect to memory function, especially using tasks that are analogous to those which reveal a similar memory deficit in AD and KS subjects. The MB are also connected to the HF (although not by the cholinergic system) and are implicated in the memory impairments of KS. A closer examination of the role of the MB in memory is thus also likely to be of value. What is more, the MB lesion serves as an interesting comparison to lesions of the MS. It was suggested earlier that the MS may be an important locus of the disruption in memory caused by AD, KS and anticholinergic drugs, and that some of the effects of hippocampal damage arise because of reduced cholinergic activity in that structure. Therefore, damage to MS which is directly involved with the supply of HF acetylcholine will result in memory impairments that are different from those produced by lesions to regions that are anatomically connected but do not consitiute part of the cholinergic input to the HF (e.g. the MB). Thus, further comparison of MS and MB lesions effects and the memory disruptions observed in AD and KS would be informative.

Although many of the lesion studies discussed in Sections 1.2.3 and 1.2.4 supported the relevant pharmacological and human clinical data which indicated that the MS and MB regions are of interest with respect to memory function, few of these studies investigated the effects of MS and MB lesions in the same study or even using the same procedures. Furthermore, the comparison of the lesion-study findings with the relevant human research has not often been attempted. This lack of integration within the nonhuman research and between the nonhuman and human experimental research generally, with respect to brain region function, makes it difficult to draw comparisons in terms of the functional similarities or differences of the MS and MB

brain regions. Consequently, the comparative roles of these brain structures in memory can only be indirectly inferred from diverse sources. Thus, an investigation of the neurological bases of memory via an examination of MS and MB lesion effects in rats must consider methods which will allow for useful comparisons between these lesion groups and with existing human and nonhuman data in order to arrive at a congruent account of brain region function.

The procedures chosen to assess the comparative effects of lesions on memory are likely to be of greater value if they are analogous to those used in the human research and thus allow similar distinctions to be made regards function. A number of the procedures used to demonstrate a memory deficit in rats following surgery are not analogous to those used with human subjects and nor are their results easily interpreted in terms of the theoretical distinctions often made in human memory research. For example, a number of animal studies confound learning of a task with memory when assessing lesion effects in terms of rate of task acquisition (e.g. a number of studies using the Morris Water Maze). Although the rate of acquisition will depend on memory it also depends on a number of other factors which may influence learning, such as learning to discriminate between stimuli and habituating to a novel situation. Also, human research often involves a distinction between various components of the memory process (e.g. delay-independent processes such as encoding and retrieval and delay-dependent processes such as retention). For this reason, performance over a range of delays is often measured (e.g. DMTS, Brown-Peterson) to separate out these various aspects of memory performance. However, the 8-arm maze task and Morris Water Maze tasks are designed to assess different 'types' of memory (e.g. spatial versus nonspatial, or trial-dependent versus trial-independent) rather than the individual components of behavior that are thought to constitute memory performance. Subsequently, interpreting the results of these traditional nonhuman memory distinctions in terms of those made in the human research is not always possible. For example, trial-independent (or working memory) measures of accuracy rely on both delay-dependent and delay-independent aspects of

performance, and disruption to either or both aspects will impair working memory performance. Greater congruence between methods used with humans and nonhumans is essential if researchers wish to draw upon both the human research and animal studies in order to arrive at some conclusion of the roles played by various HF connections in memory.

A review of the relevant human research (Section 1.1.1) revealed that certain methods of investigating memory are likely to be of value when investigating the effect of CNS cholinergic disruption (either in human clinical disorders or via pharmacological investigations). Two types of procedure have been used extensively to demonstrate and explore memory disruptions in humans suffering from AD, KS and under the influence of general cholinergic blockade are, 1. procedures which have allowed an investigation of the memory for list items, and 2. procedures which have allowed an assessment of forgetting rate over a range of delays. Thus, these two types of procedure are likely to be of value in exploring the effect of hippocampal cholinergic disruption (via MS damage) against the effects of damage in other structures connected to the HF (i.e. MB); and comparing the effects of both to the memory disruptions in AD, KS and under a general pharmacological reduction in acetylcholine. In this respect, two analogous procedures which can be used with rats are the radial-maze SPR and automated DMTS tasks. However, there have been no systematic attempts to compare the effects of MS and MB damage and there have been very few attempts to examine SPR and DMTS performance in these groups separately. (Some studies have examined MS lesion effects in SPR, and there are no published accounts of MB lesion effects in this task. Conversely, there have been a few studies to explore MB lesion effects in DMTS, but there is no published research on MS lesion effects). Therefore, the present research examined performance in both MS and MB damaged rats using SPR and DMTS tasks in order to make systematic comparisons between lesion effects and to provide comparability with the list-memory tasks (e.g SPR and free recall of list items) and delayed conditional discrimination tasks (e.g. DMTS and Brown-Peterson) used with humans.

The discussion will now review the relevant previous research which has used variations of the SPR and DMTS procedures. Section 1.3.1 will discuss the use of the SPR task in the radial maze to explore list memory in rats, and Section 1.3.2 will discuss the use of DMTS tasks and analytical techniques to explore memory performance, with and without the presence of potentially interfering events.

1.3.1 Memory for List Items in Intact and Lesioned Rats

Section 1.3.1 explores two major issues. The first issue is concerned with findings of the previous research which has examined memory for list items in brain-lesioned rats. It is concluded that the interpretation of lesion effects in many SPR studies is hampered by the existence of weak primacy and recency effects prior to surgery. The second part of Section 1.3.1 elaborates on the major issues which need to be addressed with intact rats prior to conducting an investigation of lesion effects on memory for list items.

The Effect of Medial Septum Lesions on Memory for List Items

The examination of lesions on the primacy and recency effects (jointly referred to as the Serial Position Effect - 'SPE') in rats has been investigated using the SPR procedure. Typically, a SPR trial consists of two phases: a presentation phase in which a list of items is presented, and a test phase in which recognition is tested for a single item from the list versus a distractor item. Previous attempts to demonstrate a SPE in rats have usually examined memory for lists of arms presented in an 8-arm radial maze. However, while there have been many radial-arm maze studies with MS-lesioned rats, only two of these have examined performance as a function of list-item position (Kesner et al.,1988 and Kesner et al., 1989). The effect of MB lesions on SPR performance has not been studied at all.

Kesner et al. (1988) examined the effect of various brain lesions on SPR performance using a list of 5 arms presented in an 8-arm maze and a matching rule in the test phase. After a rat had visited each list arm, recognition for one of those list

arms was assessed by providing the rat with a choice between a previously seen list arm and a novel, non-list arm. The main results from Kesner et al. (1988) are reproduced in Figure 1.5.

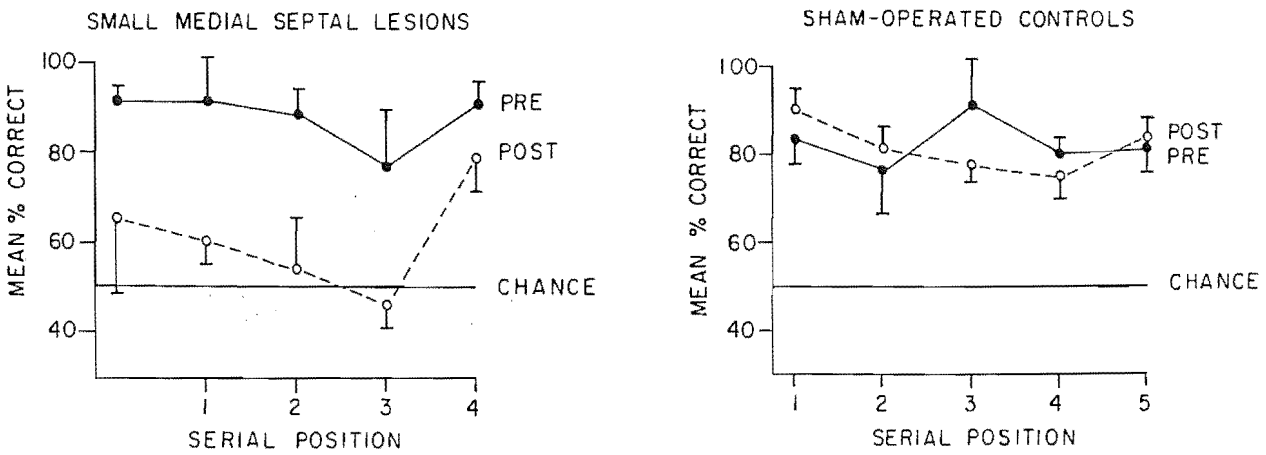

FIG 1.5 Shows the effects of small MS and sham lesions on SPR performance from Kesner et al. (1988). Filled circles are pre-surgery performance, and open circles are post-surgery. On the x-axis is the serial position of list items, and on the y-axis is the mean percentage of correct recognition trials for the group.

Figure 1.5 shows that the six rats with a relatively large MS lesion displayed an impairment in recognition at all serial positions in the list. Four other rats, with a relatively small MS lesion, showed no significant impairment at the final list position but were significantly impaired at all positions earlier in the list. That is, rats with relatively small MS lesions were similar to people with mild AD and KS in that performance for early and middle positions of the list was more impaired than for final list positions. The effect of MS lesions demonstrated by Kesner et al. (1988) were replicated by Kesner et al. (1989), who also showed that NBM lesions did not result in an impairment in this

SPR task. Thus the two studies by Kesner and colleagues further implicate the MS, but not NBM, in the memory deficits observed in AD, KS and under the presence of anticholinergic drugs. However, this apparent effect of MS lesions on the SPE is not without ambiguity in these studies. Prior to surgery, neither the control group or the small MS group displayed a SPE with primacy or recency evident. Therefore, concluding that MS damage results in a loss of primacy but a retention of recency is beyond the scope of the results since these effects were never present in the first place.

The Demonstration and Nature of the Serial Position Effect in Rats

Although evidence suggests that an examination of MS and MB lesion effects on the SPE in rats may be worthwhile, there are two issues which need to be addressed prior to this. Firstly, the SPE itself must be shown to be clearly evident in rats prior to surgery. Second, if the basic SPE can be convincingly obtained with rats then it also needs to be shown that it is analogous to the SPE observed in humans.

With respect to the first issue, the lack of a clear SPE in Kesner et al's (1988) study might seem unusual in that they used a procedure which has been previously shown to produce a very clear SPE (DiMattia & Kesner, 1984). However, a closer inspection of the published data indicates that the absence of clear SPE's is the rule rather than the exception whilst using the 8-arm maze procedure described above. For instance, a number of other studies conducted by Kesner and colleagues, in which the effects of lesions on the SPE were investigated, have not reported presurgery performance (e.g. Kesner et al., 1989) or have failed to replicate the strong SPE observed by DiMattia & Kesner (1984) despite similar procedures (e.g. DiMattia & Kesner, 1988; Kesner & Beers, 1988; Kesner & Holbrook, 1987). Consequently, as with the Kesner et al. (1988) study, the apparent effect of lesions on primacy and recency in these studies is not convincing as these two features of the SPE were not evident prior to surgery or in control animals. Therefore, a necessary aspect of any further investigation on the SPE in rats needs to be the establishment of clear and robust SPE's in the first instance.

Thus, procedures need to be developed which will increase the likelihood of emergence and the clarity of both primacy and recency effects in rats.

Apart from establishing that primacy and recency effects can be obtained in rats, it needs to be established that these two aspects of performance are independent from one another, and thus analogous to the effects observed in humans. Showing this independence with rats is desirable for several reasons: Firstly, if the primacy and recency effects can be altered in animals in a manner similar to that with humans, researchers can be reasonably confident that they are dealing with similar phenomena across species and this will aid with the integration of diverse research lines. Secondly, demonstrating that the primacy and recency effects are independent would help support any conclusions regards the differential or non-differential effect of lesions on these effects. Finally, developing the procedures to alter primacy and recency effects in species other than humans would allow for a potentially more revealing study of lesion effects on the SPE. For instance, not only would it be possible to examine the effect of a lesion on the basic SPE, but also whether the disruptive (or, nondisruptive) effect of a lesion remains constant under conditions that promote enhancement (or, reduction) of primacy and recency. Thus, the investigation of the independence of primacy and recency effects in rats is a necessary component of any research effort that wishes to explore list memory / lesion interactions.

Previous research has provided considerable evidence that primacy and recency effect can be altered independently of one another in humans. Such independence can be demonstrated by showing that alterations in the memory task effect primacy and recency effects differentially. For example, placing a delay between list presentation and subsequent recall or recognition reduces the size of the recency effect, but leaves the primacy effect intact (Glanzer & Cunitz, 1966; Postman & Phillips, 1965; Wright et al., 1985). Likewise, requiring a human subject to perform a distracting task of some type between list presentation and recall also reduces the recency effect, although the primacy effect is left intact (Glanzer, Gianutsos & Dubin, 1969).

Although the demonstration of an independence between primacy and recency effects has been shown in the human research, this issue has been relatively unresearched with respect to nonhumans. As with humans it may be that delays, or performance of a task in the delay, has a similar differential effect on components of the SPE in nonhumans (Wright et al., 1985). Two studies have investigated the effect of delay on the SPE in rats. Kesner & Novak (1982) used a procedure which required rats to return to the earlier of two arms sequentially visited during presentation of all 8 arms in an 8-arm radial maze. This procedure results in a SPE because rats are accurate at discriminating between the 1st and 2nd, or 7th and 8th arm of the list, but are very poor at discriminating the 4th from 5th arm of the list. When a delay of 10 min was placed between list presentation and subsequent choice, the recency effect disappeared (i.e. poor performance at discriminating 7th vs 8th arm) but primacy was only slightly reduced. However, the relatively long delay used by Kesner & Novak does not allow for the assessment of delays that are typically employed with other species in tasks more akin to the procedures used with humans. The second study using rats was conducted by Bolhuis & van Kampen (1988) and involved the presentation of a 5 arm list in an 8-arm radial maze with variations in the delay between list presentation and recognition. However, the effect of delay on the SPE is uncertain in this study, because although accuracy for the final list position tended to decrease as delay increased, at the shortest delays a SPE was not always evident. Consequently, the effect of delay on memory for list items in rats needs closer examination. Furthermore, the influence of variables such as a disruptive event (e.g. free access to food) during the delay or the potentially beneficial effects of increased list arm exposure have not been investigated in animals performing in a SPR task. In conclusion, the existence and independence of primacy and recency effects in rats has not been convincingly demonstrated and more research needs to be conducted on this issue prior to examining lesion effects on the SPE.

1.3.2 Delayed-Matching-to-Sample Performance in Intact and Lesioned Rats

In addition to the SPR task, a second useful procedure for examining lesion effects on memory performance is the DMTS task. Section 1.3.2 covers three general issues concerned with the use of this task to assess memory function in rats. The first part recaps the basic DMTS procedure and describes some of its major benefits. The second part of the discussion focuses on the evidence from previous research which has indicated that the effects of MS and MB damage merit investigation with the DMTS task. The third part of Section 1.3.2 describes some of the analyses developed to assess DMTS performance which allow for greater sophistication in the examination of lesion effects.

The Delayed-Matching-to-Sample Task

As described in Section 1.1.1 the DMTS task generally involves a number of trials with the following sequence of events occurring on any given trial: a stimulus is presented for a period of time; the stimulus is then removed and a delay period begins; at the end of the delay the subject is presented with the original stimulus and at least one other, and has to identify the original target stimulus. The DNMTS task is essentially the same as the DMTS task except that it requires a subject to choose the stimulus that it has not just previously been exposed to in the presentation phase. There are a number of ways to present stimuli to rats in a DMTS or DNMTS task. For example, in an operant chamber lever position (e.g. Dunnett, 1985; Aggleton et al., 1991) or tones (Kirk et al., 1988) can be used. Similarly, arms in a T- or 8-arm maze (Saravis et al., 1990) or non-spatial stimuli presented in a Y-maze (Aggleton et al., 1990) have all been used. The critical aspect common to all these variations of the DMTS task is that they require subjects to perform conditional discriminations over a range of delays between the initial presentation and subsequent discrimination testing. There are two general aspects of the DMTS task that make it particularly useful in the present context of exploring lesion effects on memory. Firstly, the DMTS task allows a separation of delay-dependent from delay-independent alterations in accuracy.

Second, the DMTS task provides a basic procedure in which the effects of proactive and retroactive interference on performance in lesioned rats can be investigated.

Although there are a number of procedures used to assess the memory deficits in rats following lesions, performance in many of these tasks is not necessarily specific to deficits in memory *per se*, but may reflect delay-independent deficits in sensory or motor capacities, failure to attend to relevant stimuli, or an unspecific impairment to learning. For example, with the standard 8-arm radial-maze task the evidence that MS and MB lesions affect memory is indirect. This task does not allow an assessment of whether performance changes are reflected in terms of alterations in the rate of forgetting or whether such changes are best described as a general overall reduction in accuracy at every delay. Even the basic SPR task (without delays) discussed in Section 1.3.1 does not allow for this comparison. Using the Morris Water Maze task to assess memory performance also results in similar problems because the assessment of memory is indirect in that the behavior being measured is often rate of learning or escape latency, and therefore is not free of any one of a range of confounding 'non-memorial' behavioral changes. Similarly, alternation tasks involve not only remembering where the subject last was, but also makes use of a strong tendency in rats to alternate between options. For this reason, alternation tasks make use of behavioral patterns that are perhaps more species specific, and may be dissociable from actual memory *per se*, and may be disrupted by interventions that are assumed to affect memory.

The difference between delay-dependent and delay-independent processes has been an important distinction in human memory research (e.g. Wickelgren, 1972; Kinsbourne & Wood, 1975; Money et al., 1992; Kopelman, 1985, 1991) and is increasingly recognised in animal memory research (e.g. White & McKenzie, 1982; McCarthy, 1981; McCarthy & White, 1987). Therefore, the MS and MB brain regions need to be examined in rats with tasks which assess rate of forgetting and allow for a separate assessment of the various aspects of performance that may influence overall

accuracy. The DMTS task, because it examines recognition performance over a range of delays, can achieve this separation. Performance at no delay between item presentation and recognition provides a measure that is free of any decay in accuracy due to forgetting and hence reflects the operation of delay-independent behavior. Whereas, the slope of the change in accuracy over delays provides a measure of rate of forgetting that is, delay-dependent changes in performance.

Apart from allowing an informative separation of delay-dependent and delay-independent aspects of performance, the DMTS task provides a useful context for the examination of proactive and retroactive interference effects. As indicated in Section 1.1.1, the investigation of interference effects on memory performance may be informative in terms of more greatly specifying the memory impairments following brain damage. The human research presented in Section 1.1.1 indicated that a feature of AD and KS is the high degree of susceptibility to the interfering effects of events which occur during and prior to the current trial (i.e. retroactive and proactive sources of interference - e.g. Morris, 1986; Sullivan, Corkin & Growdon, 1986, Butters, 1985; Butters et al., 1987; Delis et al., 1991; Kramer et al., 1988). Comparatively, there has been very little research conducted exploring interference effects with animals following lesion damage. The automated DMTS task provides a useful tool to rectify this situation because it allows precise control over variables which influence memory performance (e.g. the arrangement of events in the delay and the interval between trials). Indeed, there is already a considerable body of data from studies with intact pigeons and rats which has explored various sources of interference on DMTS performance and thus provides a good starting position for exploring the combination of lesion effects and interference (e.g. White, 1985; Edhouse & White, 1988; Roberts & Grant, 1978; Jans & Catania, 1980; Dunnett & Martel, 1990).

Lesion Effects on DMTS performance

Various DMTS procedures have already been usefully employed to examine a variety of memory deficits following lesions or pharmacological disruptions to the

cholinergic system (e.g. NBM lesions - Dunnett, 1985; Dunnett et al., 1989; fimbria-fornix lesions - Dunnett, 1985; Etherington, Mittleman & Robbins, 1987; Aggleton et al., 1991; and i.p. injections of scopolamine - Dunnett, 1985; Kirk et al., 1988). As with memory for list items, it is of interest to examine whether MS damage will produce impairments in DMTS performance, since AD, KS and anticholinergic drugs all produce qualitatively similar disruptions in this task. The effect of MS damage on DMTS tasks has not directly been investigated to date. However, indirect evidence which suggests that MS damage will produce impairments on DMTS tasks comes from studies which have investigated the effect of MS damage on delayed alternation. For example, Thomas & Brito (1980) found that delayed alternation in a T-maze was unaffected by septal damage at no delay between runs, but at 90 s performance was disrupted. Similarly, Hepler et al. (1985a) found that rats with combined NBM and MS damage showed greater impairment in a T-maze discrimination task relative to controls at a 10 min delay, but were unimpaired at a 5 s delay. Thus, the effect of MS damage on retention of stimuli over a range of delays has not been adequately investigated to date.

Other lines of evidence which suggest that MS damage may result in DMTS task impairments come, also indirectly, from a consideration of scopolamine and fimbria-fornix lesion effects. While evidence from the pharmacological studies indicates a delay-independent disruption to performance, the results from the relevant fimbria-fornix studies indicates a delay-dependent disruption. Thus, it is possible that a MS lesion may result in an impairment in DMTS performance, but it remains unclear what the exact nature of such an impairment might be. These two lines of research will now be discussed.

Because a lesion of the MS will result in a disruption of acetylcholine activity in the HF, the effect of pharmacological cholinergic blockade may provide an indication of whether a MS lesion might be effective in disrupting DMTS performance. The effects of CNS cholinergic blockade on DMTS performance have been investigated in several studies by comparing performance in rats given injections of the CNS-active blocker

scopolamine with rats given methyl-scopolamine (which does not cross the blood-brain barrier, and hence controls for peripheral drug effects). Dunnett (1985) trained rats in a DMTS procedure which used retractable levers in an operant chamber as matching stimuli. Each trial began with either of two retractable levers being inserted into the chamber. The lever retracted after a single response to it, and a delay of 1 to 16 s commenced. During the delay the rat was required to respond with 'nose pokes' on a panel covering the food tray. The first nose poke after the delay had timed out resulted in both levers being inserted into the chamber. A response on the lever originally presented produced a food pellet, whereas a response on the other lever resulted in a 5 s time out.

The results from Dunnett's (1985) study are shown in Figure 1.6. As expected the results show that as delay increased, the percentage of correct responses decreased. Dunnett (1985) also found that as the dose of scopolamine increased from .125 to 1.0 mg/kg there was a progressive reduction in overall percent correct, but accuracy did not decrease differentially for any delay compared to the methyl-scopolamine group. That is, there was a delay-independent decrease in accuracy, not a delay-dependent change. These results imply that cholinergic blockade throughout the brain (not just in the HF) interferes with performance via a disruption to delay-independent processes rather than via an increase in the rate of forgetting.

Consistent with Dunnett (1985), a decrease in delay-independent accuracy, but no change in the rate of forgetting, was also shown by Kirk et al. (1988) using scopolamine-treated rats. Their study was of particular value because of the use of performance measures derived from Signal Detection Theory, which eliminated the confounding influence of response bias and because the use of a quantitative model fitted to their data provided measures of rate of forgetting and a delay-independent measure of performance. These measures are discussed in more detail below.

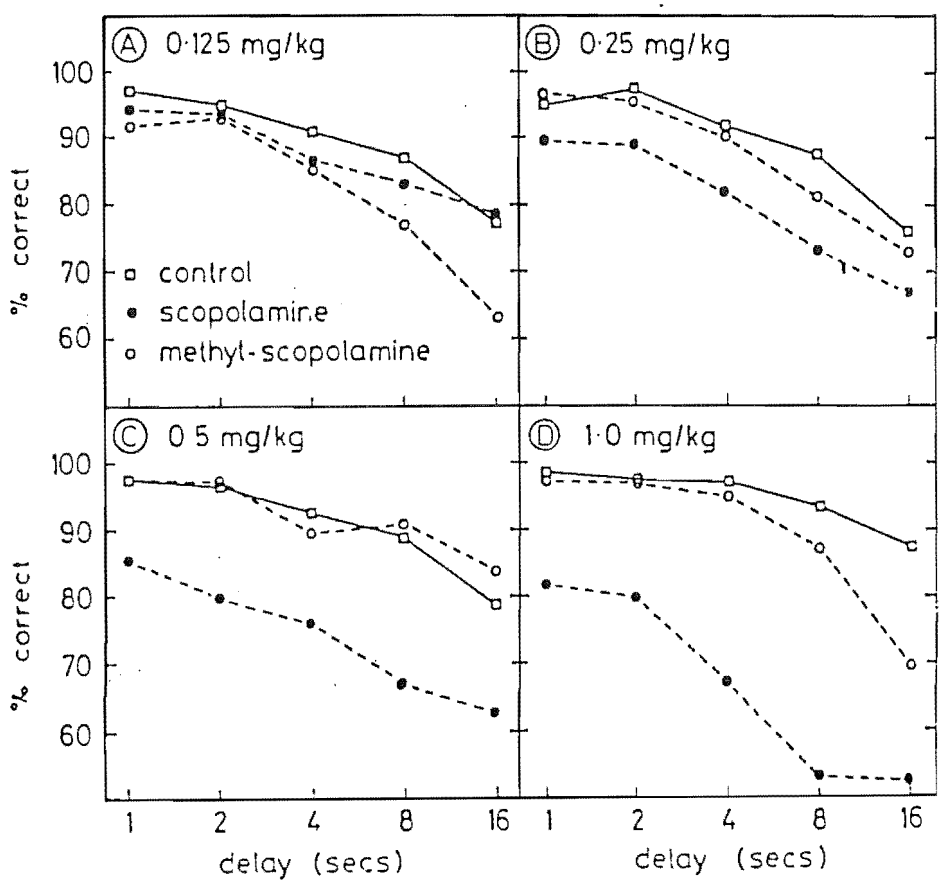

FIG 1.6 The effect of scopolamine dose level on DMTS performance in rats from Dunnett (1985). Each panel is a different dose level, and shows data for all rats averaged following saline (open squares), scopolamine (filled circles) and methyl-scopolamine (open circles) injections. The x-axis is the delay in sec., and the y-axis is percent correct.

Although the effects of cholinergic blockade on DMTS performance implicates brain regions involved in the regulation and use of acetylcholine, such as the MS, the effects of cholinergic blockade are not specific to any one region. Another source of indirect evidence for the potentially disruptive effect of MS lesions on DMTS performance comes from studies which have examined the effects of fimbria-fornix lesions. The fimbria-fornix provides contact between the HF and a variety of brain structures. Amongst these connections are fibres projecting from the MS to the HF, and fibres projecting from the HF to the lateral septum. Therefore, lesioning the fimbria-fornix will disconnect the MS from the HF, although the effect of this lesion will not be specific to the MS-HF connection. Dunnett (1985) in the same study that investigated the effects

of scopolamine on DMTS performance, also investigated the effects of fimbria-fornix and NBM lesions. Dunnett found that although performance in the fimbria-fornix lesioned group was unimpaired at a 1 s delay, as the delays increased performance became increasingly impaired relative to controls. That is, fimbria-fornix lesioned rats displayed a delay-dependent reduction in accuracy (i.e. increase in the rate of forgetting). However, rats with a NBM lesion showed an constant impairment at each delay (including 1 s) compared to controls. That is the NBM group were impaired in terms of a delay-independent reduction in percent correct, not an increase in the rate of forgetting. The effects of these lesions on DMTS performance in Dunnett (1985) are shown in Figure 1.7.

Etherington et al. (1987) and Aggleton et al. (1991) have used tasks similar to Dunnett (1985). Etherington et al's results showed that at delays greater than 0 s, rats with a fimbria-fornix lesion are impaired relative to controls. However, interpretation of their results is made difficult because of the lack of systematic changes in their data across delays and groups. For example, rats in the fimbria-fornix lesion group performed better at the longest delay than any other delay (except the 0 s delay). Furthermore their control rats, whilst performing at the same level as fimbria-fornix lesioned rats at no delay, perform significantly worse than rats with a NBM lesion at this point. Clearer results, which were more consistent with Dunnett (1985), were obtained by Aggleton et al. (1991). They demonstrated that relative to controls, rats with lesions of the fimbria-fornix showed a greater rate of forgetting lever stimuli in an automated DNMTS task over the range 0 to 64 s. A particular advantage of their study was the use of the bias-free measures (described below) to assess accuracy.

Thus the results of the fimbria-fornix studies (which physically separate the MS from the HF) indirectly suggest that a MS lesion may impair DMTS task performance in a delay-dependent fashion. However, the pharmacological disruption of CNS cholinergic activity (which interrupts neurochemical transmission between the MS and HF, as well as other cholinergic pathways) results in a delay-independent disruption to

DMTS performance. Therefore, while MS damage may cause a disruption to DMTS performance, the actual nature of this possible impairment is unknown.

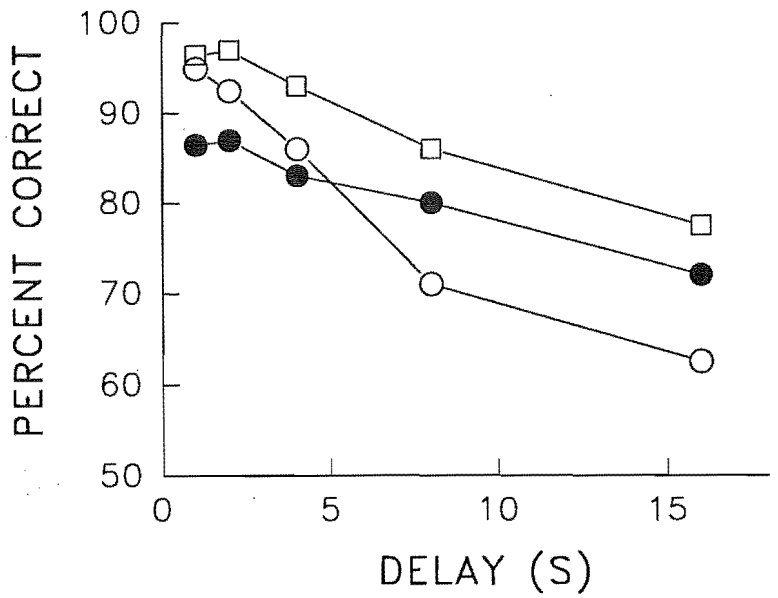

FIG 1.7 Shows the effect of fimbria-fornix (FF)- open circles, NBM (NBM)- filled circles and control-sham- open squares rat brain lesions on performance in a DMTS task redrawn from Dunnett (1985). Data points represent the mean accuracy of each group at a given delay. The x-axis is delay in sec., and the y-axis is percent correct.

In contrast to the paucity of direct MS-lesion research, there have been a number of attempts by researchers to investigate the effect of MB lesions on delayed conditional-discrimination task performance in rodents. Tako, Beracochea & Jaffard (1988) made use of a T-maze alternation procedure to examine performance in MB-lesioned rats over a range of delays. Tako et al. placed mice with MB lesions in a delayed spontaneous-alternation procedure that began each trial with two forced entries to one arm of a T-maze. After delays of 5 min or 6 hr, the subject was given a choice between both arms in the T-maze. Whereas controls showed a strong tendency to alternate (i.e. choose the arm opposite to the one originally presented) at both 5 min and 6 hr, subjects with a MB lesion alternated at the 5 min delay but chose randomly

between the two arms at the 6hr delay. Therefore, there was evidence in this study of a delay-dependent impairment in performance in the lesion group that may have arisen because of a greater rate at which MB-lesioned mice forget where they have previously been. However, contrary to the delay-dependent findings on spontaneous alternation, Saravis et al. (1990) found that MB rats possessed a delay-independent impairment in performance with an 8-arm maze DNMTS task. Saravis et al. allowed rats to choose a single arm in a presentation phase, then after a delay of 15 to 60 s, the rat was allowed to choose between this original stimulus arm and a novel arm. They found that rats with a MB lesion were impaired at all delays relative to the control group. However, it cannot be determined from their study whether an increase in the rate of forgetting might also have occurred because performance was severely reduced even at the shortest delay to such a level that did not allow for further reductions in accuracy. Consequently, the nature of the memory deficit in maze-based procedures following MB damage is uncertain. Furthermore, the issue is made more complicated by the lack of performance deficit shown by some researchers using the 8-arm radial maze task to examine working and reference memory (e.g. Jarrard et al., 1984).

The effect of MB lesions has also been investigated in other versions of the DNMTS procedure, these studies indicate that MB lesions may not result in a performance deficit. Aggleton et al. (1990) used a Y-maze to present non-spatial stimuli to rats with MB lesions. At the start of each trial a rat chose one of the arms, which differed in terms of the stimuli placed in a goal box at the end. The rat was confined to this arm for 20 s, during which the goal boxes in the two other arms were replaced. A central access door was then raised revealing a familiar box (i.e same as one currently confined in) and a novel box in the other. The rat received food if it entered the novel box, that is if it non-matched to sample. Delays were imposed by removing the original goal box after 20 s confinement, and replacing it with a featureless goal box for the duration of the delay. Using this procedure, Aggleton et al. (1990) failed to find an impairment in MB-lesioned rats relative to control rats, at any delay. The lack of effect following MB lesioning on DNMTS performance was replicated

by Aggleton et al. (1991) using an automated procedure in which rats were presented with either of two levers in an operant chamber. Following a delay of 0 to 64 s, the rat had to choose the lever which was not originally presented. As with the procedure used by Dunnett (1985), during the delay rats had to operate a flap over the food dispenser. The results from Aggleton et al (1991), presented in Figure 1.8 showed that the MB rats were only mildly and nonsignificantly impaired relative to control rats at all delays. However, rats which received a fimbria-fornix or anterior thalamus lesion were relatively more impaired than controls and MB rats at delays greater than 0 s. Thus, there have been a number of studies which have examined the effects of MB lesions on memory tasks over a range of delays, but the results are equivocal and seem to be dependent on the procedures used.

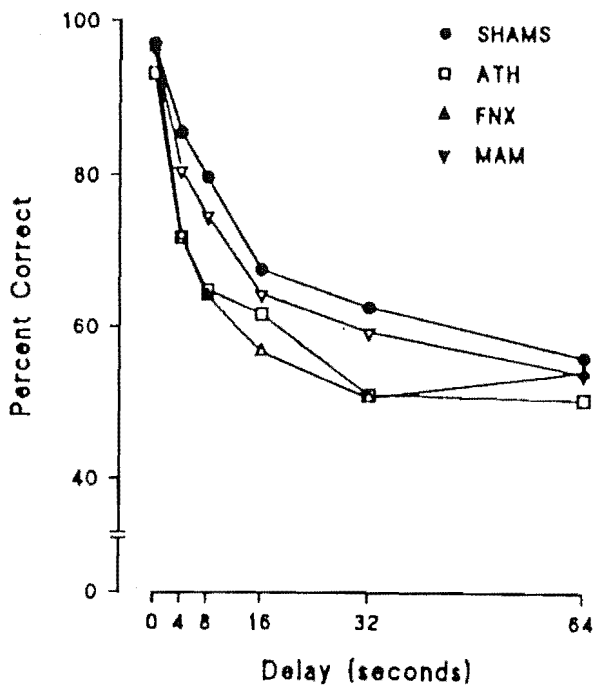

FIG 1.8 Shows the effects of sham, anterior thalamus (ATH), fimbria-fornix (FNX) and mammillary body lesions (MAM) rat brain lesions on DMTS performance from Aggleton et al. (1991). Data points show the mean percentage of accuracy for each lesion group at a given delay. The x-axis is delay in sec., and the y-axis is percent correct.

The above discussion of previous DMTS and DNMTS lesion studies indicates that a useful aspect of these procedures is that they allow a separation of delay-dependent and delay-independent aspects of performance. Another advantage of these procedures is that they allow the systematic investigation of interference effects on memory. However, previous research has not tended to investigate the sensitivity of lesioned rats to the disruptive influences of interfering events on memory. Yet such investigations are desirable because a requirement in determining the role of brain regions in memory is not just to examine performance changes post-surgery, but also the lesion / performance interactions when aspects of the task are changed. For instance, it may be that rats with damage in the MS or MB regions are more susceptible to the interfering effects of events imposed during a delay or proactive interference from previously occurring trials and learning, as shown in humans with neurodegenerative diseases which include damage in the MS (AD and KS) or MB (KS) regions.

There is now a considerable body of data with respect to the effect of various procedural manipulations on DMTS performance with intact rats and pigeons. It has consistently been shown that presentation of an event (e.g. free food access or a houselight) in the delay of a DMTS trial reduces accuracy (e.g. Jans & Catania, 1980; White, 1985). Likewise, reducing the inter-trial interval, causes progressively impaired performance (e.g. Maki, Moe & Bierley, 1977; Roberts, 1980; Edhouse & White, 1988; Dunnett & Martel, 1990). However, the effect of such manipulations have not been investigated in the DMTS procedure with rats that have received lesions. Because there are indications that these manipulations are important aspects of memory performance in both intact animals and in humans with neurodegenerative disorders it is possible that a more comprehensive picture will result if an investigation of susceptibility to interference is included in a study of lesion effects.

In summary, the DMTS task has been used to assess a variety of lesion and drug effects on memory performance in rats. However, a systematic comparison of MS and

MB lesion effects has not been made, and indeed there is very little relevant research on MS lesion effects. Similarly, there have been no comprehensive attempts to assess the influence of various sources of interference on performance in rats with lesions.

The Analysis of DMTS Performance

The lack of studies which have assessed lesion effects using the DMTS task is unfortunate because a particular advantage of using this procedure is that there has been a considerable amount of fundamental research conducted with it. This research has resulted in greater sophistication in the measurement and analysis of memory performance than is routinely employed with data from many other procedures. In particular, two developments concern, 1. the way to deal with the problem of response bias in measuring accuracy of recognition, and 2. the quantitative analysis of DMTS performance in terms of higher-order variables describing the delay-dependent and delay-independent aspects of recognition.

On any given DMTS trial a subject makes a choice between simultaneously available alternatives, and accuracy of recognition is normally measured using the percentage of correct choices. However, percent correct has two problems when used to measure accuracy. First, as recognised by a number of authors (e.g. Sahgal, 1987; Frey & Colliver, 1973; McCarthy & White, 1987) percent correct does not allow for the effect that response bias may have on accuracy. For example, a rat may choose the left lever because of a preferred smell associated with that lever, rather than an actual memory for the left lever. Therefore, percent correct scores do not differentiate between responses that occur as a result of extraneous influences and the actual 'memory component' of the task. A second problem is that percent correct is on a bounded scale, and therefore may obscure differences in performance at high overall accuracy. Many DMTS studies report high accuracy (e.g. 90 - 100 percent) for all subjects at short delays. Thus, the usual measure of percent correct can lead to erroneous interpretation of performance in the DMTS task through the confounding

effects of bias and its failure to distinguish between different performances at high accuracy.

A number of performance measures have been proposed that are derived from Signal Detection Theory (Green & Swets, 1966). Of interest in the present discussion are measures which have received empirical support for their use in measuring DMTS performance, especially with regard to examining the effects of physiological manipulations. Signal detection analyses require the conditional probabilities of correct and error responses obtained in a two-stimulus choice study. For example, in a procedure which presents either a left or right lever as the to-be-remembered sample stimulus and then requires the subject to choose that original stimulus when presented with both left and right levers, response data will fall into one cell in the following matrix:

		RESPONSE	
		Left	Right
STIMULUS	Left	C1	E1
	Right	E2	C2

FIG 1.9 The stimulus-response matrix for a two-choice detection task using levers as stimuli. 'Left' and 'Right' refer to the left and right levers respectively. Only when the response is correct (C1 and C2 in the case of matching to sample) does the animal gain reinforcement. In most studies, errors (E1 and E2) do not normally result in access to reinforcers.

Two non-parametric analyses of the data obtained from the matrix in Figure 1.9 have been proposed for use with rats in DMTS experiments (Frey & Colliver, 1973; Sahgal, 1987). By taking the proportion C1/(C1+E1) and E2/(E2+C2), called *h* and *f* respectively, these workers suggested the following two measures of accuracy:

$$A' = .5+[(h-f)+(h-f)^2/[4h(1-f)]$$

and

$$SI = [h-f]/[2(h+f)-(h+f)^2]$$

The advantage of these two measures is that they are 'bias free'. That is, the manner in which they are calculated takes account of any asymmetrical tendencies of a subject to respond on one lever as opposed to the other, independently of the sample stimulus presented. However, despite this advantage and their demonstrated applicability to lesion effects (e.g. Aggleton et al., 1991) there is still the disadvantage that *A'* and *SI* are, like percent correct, bounded measures such that at high levels of accuracy, there is minimal separation between data points.

An alternative bias-free performance measure that has gained considerable empirical support is that proposed by Davison & Tustin (1978). Davison & Tustin's analysis provided a measure of accuracy, *Log d.* This is similar to *d'* in signal detection analysis but has an empirical basis in the generalized matching law (Baum, 1974), and therefore describes the role of reinforcers in a quantitatively accurate way. Moreover, for *Log d* there is an existing quantitative model to describe the effect of delay on accuracy. Like *A'* and *SI, Log d* is calculated using the frequency of events in the stimulus response matrix shown in Figure 1.9:

$$\text{Log d} = .5 \log (C1/E1 \cdot C2/E2)$$

and response bias *Log c*, is given by:

$$\text{Log c} = .5 \log (C1/E1 \cdot E2/C1)$$

Log d is bias free (bias is quantified separately) since the calculation takes into account any tendency of the subject to prefer responding to one stimulus over the other. This response bias is confounded with error responses in percent correct measures. Table 1.1 gives an example of the calculation of *Log d* and *Log c* in respect of two stimulus-response matrices one with response bias present and the other with none. In particular, Table 1.1 shows that different degrees of response bias (*Log c*) result in different values for percent correct, even though accuracy (*Log d*) is the same.

TABLE 1.1 Comparison of percent correct and *Log d* under low and high response bias. The values in the stimulus-response matrix correspond with the cells given in Fig. 1.9.

STIMULUS-RESPONSE MATRIX		PERCENTAGE	Log d	Log c
183 (C1)	17 (E1)	91.5	1.03	0
17 (E2)	183 (C2)			
196	4	84.0	1.03	.66
60	140			

When *Log d* = 0, performance is at chance level, thus the higher the value of *Log d* - the higher is bias-free accuracy. *Log d* and *Log c* are both non-bounded since they are ratios, and hence may reveal differences in behavior that are hidden using bounded scales when behavior is at high levels of accuracy. Furthermore, there is now considerable experimental evidence which supports the use of *Log d* as being a valid measure of performance in discrete-trial psychophysical experiments and free-operant multiple-concurrent discrimination tasks (McCarthy & Davison, 1984; McCarthy, Davison & Jenkins, 1982; McCarthy & White, 1987).

An important use of *Log d* and *Log c* has been in the assessment of DMTS performance and the subsequent development of quantitative models which describe changes in accuracy and bias with changes in delay. When fitted to data using regression analyses, these models provide empirically determined descriptions of two separate factors in memory performance: those which are delay-dependent (i.e. alterations in accuracy across delays, typically referred to as rate of forgetting which reflects actual memorial retention *per se*) and delay-independent (i.e. alterations in 'encoding' or 'retrieval' processes that are assumed to be independent of memorial retention and exert a general influence on accuracy at all delays). The typical finding of studies has been that as delay increases, the measure of *Log d* decreases in a regular monotonic fashion described by either a negative-exponential function (e.g. White &

McKenzie, 1982; White, 1985), or a hyperbolic decay function (McCarthy, 1981; McCarthy & White, 1987). For example, White & McKenzie (1982), using pigeons as subjects and wavelength as discriminative stimuli, examined the effect of delay stimulus presentation and subsequent discrimination performance. They suggested that the effect of delay on discrimination performance was to degrade the obtained values of *Log d* in a manner described by the following negative-exponential equation:

$$\text{Log } d = \text{Log } d_0 \, e^{-bt} \qquad 1$$

In Equation 1, *Log do* measures the ability to choose correctly between the stimuli at a delay of 0 s, *t* is the delay, and *b* is a constant describing the rate of decrement in *Log d* over increases in delay. Therefore, *Log do* provides a measure of delay-independent DMTS performance, and *b* provides a measure of the rate of performance decay, or forgetting across increases in delay.

McCarthy (1981) proposed an alternative model in which the rate of decay is not a constant, but instead, is a function of delay. Specifically, McCarthy suggested that the function relating changes in *Log d* to increases in delay is a rectangular hyperbolic function:

$$\text{Log } d = (h / h + t) \cdot \text{Log } d_0 \qquad 2$$

In Equation 2, *h* is a measure of the half-life, or the time *t* at which accuracy at a 0 s delay (*Log do*) decreases to one half its initial level. The parameters *t* and *Log do* have the same interpretation as in Equation 1. As with the exponential model, two free parameters are obtained by fitting the hyperbolic function to the calculated values of *Log d*; a measure of delay-independent accuracy (*Log do*), and a measure of forgetting rate (*h*).

Both Equations 1 and 2 have a great deal of support for their utility in describing DMTS performance. For example, McCarthy & White (1987) examined nonlinear least-squares regression fits of both equations to a variety of data sets. Using *Log d* measures where possible, or analogous non-bias-free measures, they commonly found that the variance accounted for and mean squared error of these functions was greater than 90 percent and less than .05 respectively. Furthermore, both models provided good descriptions of data obtained from both animal and human studies. This is especially important if our ultimate aim is to try and interpret both animal and human memory studies in similar terms to arrive at any conclusions about brain region function. However, since both models provide very good data fits and similar results, the preferential use of one model over another needs to be based on an assessment of the data set currently under scrutiny. Given that there has not yet been an attempt to compare Equations 1 and 2 over a range of conditions using data obtained from rat DMTS performance, there are no *apriori* reasons for choosing one over the other.

The advantage of both equations is that they utilise the bias-free accuracy measure *Log d* to provide two higher order measures that are of use in examining DMTS performance in rats with lesions. The first measure of performance, *Log do*, that is gained provides an indication of changes resulting from delay-independent processes. Typically such processes have been described as 'encoding' or 'retrieval' (e.g. Kirk et al., 1988). However, a hypothetical process does not need to be associated with the measure *Log do* to make it useful in the current context, since the current questions being addressed have to do with the separation of delay-dependent and -independent measures of performance rather than their theoretical interpretation in terms of theoretically-based cognitive constructs. The second measure of performance that is gained is a measure of rate of forgetting, *b* (from Equation 1) or *h* (from Equation 2). The measures *b* and *h* provide an indication of actual memory decay *per se* that is independent of initial performance levels (*Log do*) and is also free of the influence of response bias.

A working demonstration of Equations 1 and 2 can be provided by reanalysing the percent correct data of Dunnett (1985) shown earlier in Figure 1.7. An approximation of *Log d* can be gained by estimating the percentage scores from Dunnett's study and transforming them into the log ratio of correct over error responses (elsewhere referred to as *logit p*, McCarthy & White, 1987). This measure is only an approximation of *Log d*, and does not partial out response bias, but it is on an unbounded scale and will serve for the purpose of the present demonstration. Figure 1.10 shows these estimates plotted as a function of delay for three groups of rats - NBM and fimbria-fornix damaged rats as well as a control group. The two graphs in Figure 1.10 show that both the exponential function (Equation 1) and hyperbolic function (Equation 2) fitted to the data provide very good, and virtually identical summaries of the performance differences between NBM, fimbria-fornix and sham - lesioned rats.

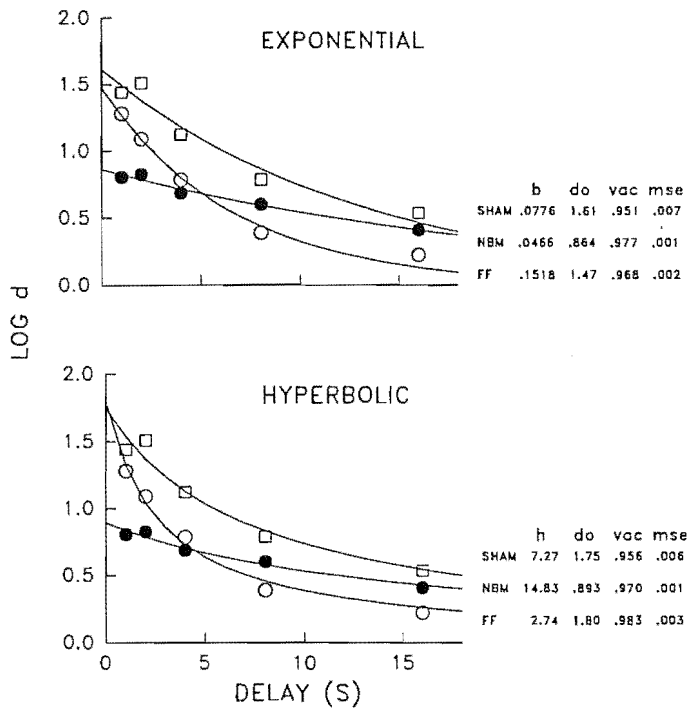

FIG 1.10 Shows the percent correct data DMTS from Dunnett (1985) reanalysed to give estimates of *Log d*, which are plotted against delay (s). Fitted to these plots using nonlinear least-squares regressions were Equations 1 (top graph) and 2 (bottom graph). Both equations provide a measure of delay-independent performance (*Log do*) and rate of forgetting (*b* and *h* respectively). Filled circles are data from rats with NBM lesions; open circles are data from rats with a fimbria-fornix lesions; and open squares are from control-sham rats.

The NBM group in Figure 1.10 provide an example of a reduced value for *Log do* (i.e. an impairment in delay-independent performance). Graphically, this appears as a lower Y-axis intercept of the function obtained for the NBM group compared to the control group. Figure 1.10 also shows the effect on the forgetting function that results from a difference or change in the rate of forgetting. Rats which received a fimbria-fornix lesion were similar to the control group in the obtained measure of *Log do,* but they displayed a much greater rate of forgetting (i.e. higher values for *b* and lower values for *h*). Graphically, this appears as a divergence of the functions obtained for the control and fimbria-fornix groups. The present reanalysis of Dunnett (1985) demonstrates that use of Equations 1 and 2 may provide extremely good summaries of DMTS performance in both intact and lesioned rats. Despite the advantages of this approach, the separate delay-dependent and delay-independent aspects of memory performance quantified by fits of these two equations have not been studied with respect to lesions of the MS and MB.

1.4 THE PRESENT RESEARCH

The present research sought to develop further our knowledge of the neurological bases of memory by investigating the effects of MS and MB lesions on memory task performance. The review of the literature (Sections 1.1 to 1.3) indicated that there is considerable evidence implicating the MS and MB brain regions in memory function, but little available data which allows for a direct comparison of their role(s). This review also indicated that two methods of assessing memory, SPR and DMTS, may be informative when comparing the MS and MB regions. Thus, two general considerations shaped the current studies - 1. the choice of which brain regions to investigate, and 2. how to investigate their role(s) in memory. These two considerations are summarised below.

With respect to the choice of brain regions studied, there are several converging lines of evidence from both the human and nonhuman research that the MS brain region may play a role in memory function. Research on humans with AD and KS shows that they exhibit a number of similar memory deficits. For example, when required to recall or recognise list items, the primacy effect is eliminated or severely reduced, yet the recency effect remains either intact or only slightly reduced. Subjects with these disorders also show impairments in memory when assessed using tasks that examine performance over a range of delays (e.g. DMTS, delayed recall and Brown-Peterson tasks). Damage in the MS is a neuropathological feature common to both disorders. So, it may be that AD and KS subjects exhibit such memory disruptions because of neurological damage in the MS region with a resultant loss of acetylcholine activity in the HF.

Consistent with the potential role of the MS in memory (via the supply of acetylcholine to the HF) are the human and nonhuman studies which have shown that anticholinergic drugs result in a similar pattern of memory disruptions shown by AD and KS. For example humans given scopolamine show a reduction in primacy, but retention of the recency effect; as well as deficits in DMTS performance. Similarly, rats given scopolamine show impairments in a variety of memory tasks such as the standard 8-arm radial maze, T-maze alternation, the Morris Water Maze and DMTS. Also consistent with the experimental pharmacological and human clinical evidence implicating the MS region in memory is a large amount of nonhuman lesion research. For instance, rats with experimentally induced damage in the MS region show a reduction in hippocampal acetylcholine and exhibit deficits in a variety of memory tasks such as the standard 8-arm maze task, Morris Water Maze and T-maze alternation. Thus, further investigation of the MS is warranted given the existence of several lines of evidence implicating this region in memory.

The investigation of the MS region with respect to memory function is also of value in helping to develop our understanding of the role(s) played by the HF and other

structures connected to it. The HF has a long tradition of being implicated in memory function. However, studies which have disconnected the HF from many of its associated structures (including the MS, and MB regions amongst others) via fimbria-fornix lesions or caused direct damage to areas connected to the HF suggest that these brain regions themselves may also be critical regions with respect to memory. Unfortunately, because lesions to the fimbria-fornix simultaneously disconnect a number of associated structures this lesion is not specifically informative with respect to any one of them alone. A comparison of lesion effects in these related structures will help develop a greater sophistication of our understanding of the system as a whole by identifying the degree to which these structures are distinctive from one another in terms of roles in memory.

Indeed, research evidence suggests that a number of brain regions, other than the MS, associated with the HF (but not part of the cholinergic supply to it) are also implicated in memory function. One such area is the MB, and the effects of damage in this region were compared against the MS data in the present research. The MB site was chosen because of evidence showing that this region is often damaged in KS subjects and because experimentally induced damage in this structure has been shown to result in memory deficits with a variety of tasks using monkeys and rats. Thus if the reduction of hippocampal cholinergic activity, as a result of MS damage, is an important causal factor in the memory disruptions exhibited, then MB damage will result in a different amount or patterns of impairment. Therefore, a comparison of the effects caused by MS or MB damage on memory performance is important and just such an investigation formed the focus of the present research.

A further implication of the human work is role of interference in the memory deficits exhibited following neurological damage. Data suggest that events which occur during a delay (retroactive interference) or prior to the delay (proactive interference) may be more influential in memory performance in clinical disorders such as AD and KS than in control subjects. Therefore, damage in brain regions such as the MS and/or MB

(implicated in these disorders) may result in a high degree of susceptibility to analogous types of interference that have previously been investigated with intact subjects. However, as with the general lack of experimental research comparing the memory deficits following lesions to these regions, there have been no comprehensive attempts to investigate the interaction between lesion effects and interference. Therefore, the investigation of the possible interaction between lesion effects and interference was also an aspect of the current research.

With respect to a consideration of tasks for assessing lesion effects and the interaction between lesion effects and interference, a review of previous procedures used to study to memory in animals suggests that many are not comparable with human memory procedures, and instead are aimed at making distinctions which do not easily allow for an integration of the human and nonhuman work. Cornmon distinctions in the rat research have included spatial versus nonspatial and working versus reference memory aspects to performance. A more successful integration between the study of lesion effects and the existing human research may be achieved by using memory tasks with animals that are analogous to those used with humans. Two general types of task which the human research indicates may be potentially beneficial in the examination of memory deficits following brain damage are: procedures to examine memory for list items, and delayed conditional discrimination procedures to separate delay-dependent and delay-independent aspects of memory performance. Such procedures were therefore used in the current research.

Two main research projects constituted the present investigation on the role of the MS and MB in memory performance with rats - the effect of MS or MB damage on memory for list items in a SPR task, and the effect of MS or MB damage on DMTS performance. The major independent variables explored in both tasks were the effects of delay, the effects of retroactive and proactive interference and the effect of either MS, MB or sham-control lesion on measures of performance. Experiments 2.1 and 2.2 developed and explored the primacy and recency effects obtained with a 12-arm maze

SPR task. This task was subsequently used in Experiment 2.3 to investigate the effects of MS and MB lesions on memory for list items. Experiments 3.1 to 3.3 used an automated DMTS task in order to separate delay-dependent and delay-independent aspects of performance in rats following damage in either the MS or MB. In addition these experiments focused on the possible interactions between lesion effects and various sources of proactive and retroactive interference on memory performance.

Chapter 2 MEMORY FOR LIST ITEMS IN RATS

Chapter 2 investigated the SPE in rats and the effects of lesions on it. Three experiments were conducted. Experiment 2.1 examined the conditions which may help to establish a clear SPE, with both primacy and recency effects present. Experiment 2.2 examined the independence, and thus similarity to humans, of the primacy and recency effects gained with rats. Experiments 2.1 and 2.2 were necessary to conduct prior to the examination of lesion effects because previous research has failed to provide convincing evidence of the existence of a clear SPE in rats analogous to that observed with humans. Experiment 2.3 examined the effects of MS and MB lesions on the SPE, thus established in rats.

EXPERIMENT 2.1 Production of a Serial Position Effect in Rats

When humans are given a list of items to remember, recall or recognition is best for items presented early in the list (the primacy effect) and late in the list (the recency effect), with inferior performance on items from the middle of the list. This pattern has been referred to as the Serial Position Effect (SPE). Attempts to demonstrate the presence of both primacy and recency in rats have usually examined memory for lists of arms presented in an 8-arm radial maze SPR procedure. Typically, a SPR trial consists of two phases: a presentation phase in which a list of items is presented, and a test phase in which recognition for a single item from the list is examined. While the recency effect is often obtained in the radial maze version of a SPR procedure, there has been difficulty in achieving convincing demonstrations of a primacy effect (e.g. Roberts & Smythe,1979; Bolhuis & van Kampen, 1988; Rawlins et al., 1992; see Gaffan, 1992 for a review). The failure of Roberts & Smythe (1979), Bolhuis & van Kampen (1988) and Rawlins et al. (1992) to observe convincing primacy effects may have been because rats were required to nonmatch to sample during recognition. DiMattia & Kesner (1984) gave rats a 5-arm list in a standard 8-arm maze and

compared performance when the correct choice was to return to a previously presented arm (matching to sample) with that when the correct choice was to enter the novel arm (nonmatching to sample). When the task required nonmatching to sample a clear recency effect was observed, but primacy was not evident. In contrast, both primacy and recency effects were clearly evident when the task involved matching to sample.

The rule governing the test phase is not the only aspect of the task which may determine the presence or absence of primacy effects. Some studies conducted by Kesner and colleagues have failed to replicate the strong SPE observed by DiMattia & Kesner (1984), despite similar procedures. For example, Kesner et al. (1988) examined the effect of various brain lesions on SPR performance using the matching rule and a list of 5 arms presented in an 8-arm maze. Prior to surgery, four of the five groups did not show a SPE with primacy or recency evident. Other lesion studies have also found either no evidence of a SPE in prelesion or control animals (e.g. DiMattia & Kesner, 1988; Kesner & Beers, 1988) or only weak SPEs (e.g. Kesner, Adelstein & Crutcher, 1989; Kesner & Holbrook, 1987) compared to those obtained by DiMattia & Kesner (1984). Consequently, the apparent effect of lesions on primacy and recency in these studies is not convincing as these two features of the SPE were not evident prior to surgery or in control animals.

The inconsistency with which SPEs are obtained means that researchers can not be confident about the effect of their lesions on memory performance. Thus more detailed investigation of the basic SPR procedure is needed to determine the conditions which establish clear, reliable and persistent SPEs. The various studies that have investigated the SPE in rats have used tasks of differing degrees of difficulty, different group sizes and amounts of training. These aspects of the SPR procedure may contribute to the inconsistencies observed and the present study is an examination of the conditions which may influence the emergence, reliability and persistence of a SPE in a radial maze.

One aspect of the SPR task that may be vital for the emergence of a SPE is task difficulty. DiMattia & Kesner (1984) suggested that the reason both primacy and recency emerged with a matching rule (rather than nonmatching to sample) in their study is that rats found this task more 'effortful', and therefore processed the stimuli more deeply. DiMattia & Kesner's results showed that rats took longer to learn the matching rule than the nonmatching one, indicating that matching was the more difficult task. In the present study, high task difficulty was arranged in an attempt to increase the chance of observing a SPE by using a 12-arm maze rather than the 8-arm maze used in previous research. A list of 5 arms presented in a 12-arm maze is a more demanding on a rat's ability to discriminate a novel from a familiar arm. In an 8-arm maze each arm is separated from an adjacent arm by 45^{o}, whereas in the 12-arm maze the difference between arms is 30^{o}. Hence, in a 12-arm maze there is less of a spatial differentiation between arms resulting in greater similarity between them than in an 8-arm maze. In Part 1 of the present study 5-arm lists were presented to rats in a 12-arm maze and the rats ability to return to a previously visited arm was examined.

A second potentially valuable means of increasing the difficulty of the SPR task is to increase task demands by increasing the list length. As most studies have used an 8-arm maze to examine list learning in rats, the typical list length has been 5 items long. To extend the list further in an 8-arm maze is problematic, as it is necessary to keep some arms unvisited in the presentation phase to be used as novel arms in the test phase. If the list length were extended too far in the 8-arm maze it would become easier for the rat to remember the unvisited arms which thereby lessens the load on memory. Consistent with this suggestion, Roberts & Smythe (1979) failed to show a primacy effect when they presented rats with a 7 arm list in an 8-arm maze. With 12 arms to draw from, the list length can easily be extended to 7 arms and still leave 5 arms unvisited. In Part 2 of the present study the list length was increased from 5 to 7 arms to assess whether the SPE is more pronounced with this increase in task difficulty. One particular advantage of the 12-arm maze is that all 5 (Part 1) or 7 (Part

2) members of the presentation list can be tested in one day, using different non-visited arms on each test trial.

An issue that needs clarification is why some studies using similar procedures are inconsistent with one another with regard to the emergence of a SPE (e.g. DiMattia & Kesner, 1984 c.f. DiMattia & Kesner, 1988; Kesner & Beers, 1988; Kesner et al., 1988). These studies differed in terms of the number of subjects used and/or the amount of training received so these aspects may be important in the emergence and maintenance of a clear SPE (Gaffan, 1992). DiMattia & Kesner (1984) had a larger group size (n=10) than the other studies (n=4-6), so perhaps the presence of a statistically reliable SPE depends having relatively high subject numbers. The influence of amount of training on the SPE is unclear because some studies have used fewer training trials (e.g. Kesner & Beers, 1988; Kesner et al., 1988) than DiMattia & Kesner (1984), while other studies have given more training trials (e.g. DiMattia & Kesner, 1988), and still failed to obtain a clear SPE. Thus, the effects of subject numbers and amount of training on the group SPE need to be investigated in more detail and this was done in the present study.

METHOD

Subjects

23 naive male Wistar rats approximately 4 months old at the start of the experiment served in Part 1; 20 of these same rats were also used in Parts 2 and 3. The rats were housed four per cage and were maintained at 80-85% of their ad libitum body weight with free access to water throughout the study.

Apparatus

The apparatus was an elevated (85 cm from the floor) radial maze, comprising 12 evenly spaced aluminium arms radiating from a wooden central platform, 35 cm wide and painted black. Each arm was 9 cm wide and 65 cm long, with 3 cm borders, a 25

cm high perspex barrier at the proximal end, and a 2 cm diameter food well drilled in a wooden block placed at the distal end. Access to each arm was controlled via a clear plastic guillotine door located between the platform and the arm. Doors could be raised singly or in combination by means of pulleys operated by the experimenter adjacent to the maze. The windowless room housing the maze was lit by two 22 watt fluorescent lamps. A door, shelves and table provided ample external cues to the maze, the position and orientation of which was kept constant.

Procedure

For an initial pretraining session, groups of rats were able to explore freely the entire maze with chocolate chips (0.1 gm) scattered over the length of all the arms. For the next two sessions, chocolate chips were available only at the end of each arm. For the next three pretraining sessions (with three trials per session) an individual rat was placed on the central platform and a randomly chosen door was lifted, allowing access to three pieces of chocolate at the end of the arm.

Performance in the matching to sample SPR task was then shaped using progressively longer lists of arms. For each of 5 sessions (with 3 trials per session), rats were presented with a single arm in the presentation phase prior to the test phase. In the following 7 sessions (with 3 trials per session), rats were presented with a 3-arm list in the presentation phase prior to the test phase. Finally, the experiment proper began with a 5-arm list presented in Part 1, followed by a 7-arm list in Part 2.

Irrespective of list length, the task involved two phases - a presentation phase in which a sequence of arms were successively available to the subject followed by a test phase in which recognition for one of the list arms was examined. At the start of a trial, a rat was placed on the central platform and all doors were lowered. A predetermined sequence of arms was then presented to the rat, one arm at a time. The door to the first arm in the sequence was raised, allowing the rat to run down the arm and gain a single piece of chocolate. When the rat returned to the central platform the door was

lowered and the door to the next arm in the list was raised. After all arms in the list sequence had been visited, one of those arms was then rebaited with three pieces of chocolate before the experimenter simultaneously raised the door to the rebaited arm and the door to an unbaited arm not visited in the previous list. The interval between the last door being lowered in the presentation phase and the two doors being raised in the test phase was approximately 5 s. The rat was left in the apparatus during the delay. In the test phase the rat was required to return to the one arm of the pair which had been visited during the presentation phase (i.e. match to sample). Once three paws had entered an arm, the door was lowered and the rat was counted as having made a response.

Sequences were chosen that did not allow for a response strategy to aid recognition of the previously presented arm (e.g. lists of arms 1, 3, 5, 7, 9 or 1, 2, 3, 4, 5 were not allowed). Comparison (previously unvisited) arms chosen for each test phase of a trial were always next door but one to the correct arm; on 50% of the trials the comparison arm was to the right of the correct arm and on the other 50% it was to the left. Sessions were run 5 days a week . In any session a rat was exposed to only one sequence, repeated for all trials in that session.

In Part 1, rats were tested for 5 trials per session. On each trial, the 5 list arms were presented and then recognition was tested for one of those arms. To allow all serial positions in the list to be tested once (for each rat in a given session), on each trial a different list arm and one of the seven nonlist arms were tested for recognition. The order of testing serial positions was varied across rats per session and within rats over sessions. After being run on a trial, the rat was removed from the apparatus and the next rat was run, until all rats had received one trial. The first rat was then run on the second trial of the session and so on until all rats had completed their 5 trials for the day. Thus, successive trials for a given subject were normally at least 20 minutes apart. The rats were trained for 30 sessions in Part 1 (i.e. 150 trials per rat testing all serial positions) . In Part 2 rats were again tested for 5 trials per session. The list length in

the presentation phase was extended to 7 arms, but only 5 positions in the 7-arm list were tested for recognition (Serial Positions 1, 3, 4, 5 and 7). Only 5 arms were tested for recognition because when presenting a 7-arm list, only 5 of the 12 arms available are left free to serve as comparison arms. Otherwise the procedure was the same as in Part 1. The rats received 15 sessions of training in Part 2 (i.e. 75 trials per rat across all serial positions).

RESULTS and DISCUSSION

The results of Parts 1 and 2 of the experiment are presented in separate sections below.

Part 1

Part 1 of the present experiment demonstrated that in a 12-arm maze, use of a 5-item list would result in a clear SPE with primacy and recency effects present. Apart from replicating the phenomenon of a SPE in rats, Part 1 extended this basic finding by demonstrating that primacy and recency were still present after a large number of training trials. Figure 2.1 shows 5 consecutive blocks of sessions in which percent accuracy in the recognition test is given for each serial position. Each data point represents the average score of 23 rats from 6 sessions of training.

In Sessions 1-6, accuracy lay between 60-70%, irrespective of serial position. A one-way ANOVA with serial position as a repeated measure showed that there was no main effect of serial position on performance [$F(4,88)<1.0$] during Sessions 1-6; nor were there any quadratic (i.e. 'U' shaped) trends apparent in the data. By Sessions 7-12, a SPE emerged because accuracy at Positions 1, 2 and 5 was generally greater than at Positions 3 and 4. That is, both a primacy and recency effect were evident. The presence of the SPE was confirmed by the existence of a significant quadratic trend in accuracy across serial positions [$F(1,22)=18.74$, $p<.01$]. Post-hoc

comparisons revealed that Positions 1, 2, 3 and 5 were all significantly different from Position 4 at the $p<0.05$ level. The only other significant difference at this level was between Positions 1 and 3. A SPE was still evident in the following two blocks of training. That is, Sessions 13-18 and 19-24 continued to show a significant quadratic trend across serial positions [$F(1,22)=6.4$, $p<.05$ and $F(1,22)=8.34$, $p<.05$ respectively].

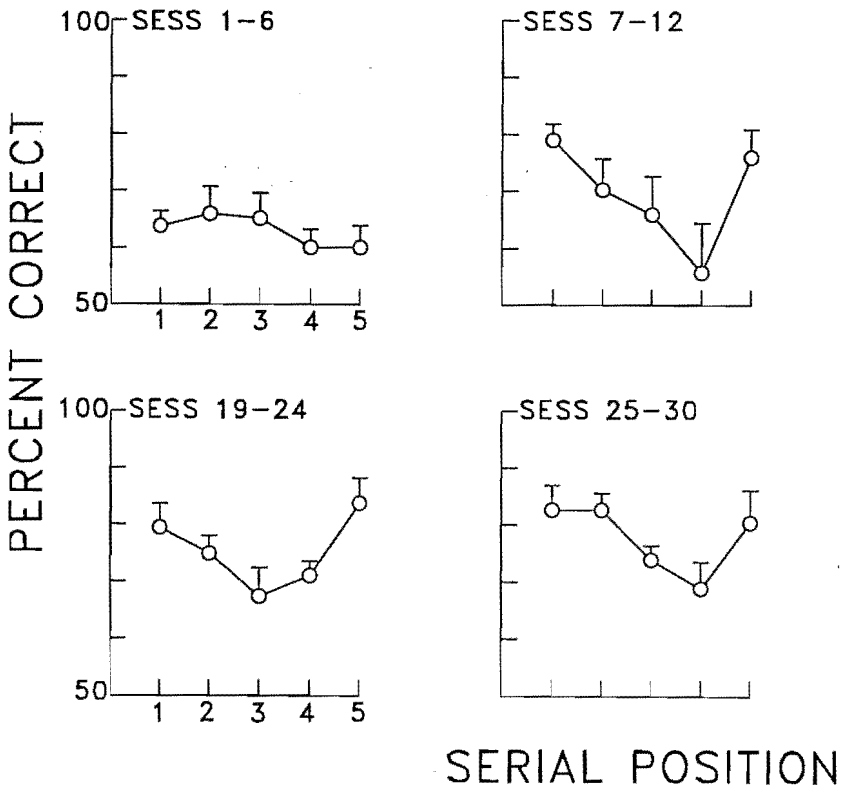

FIG 2.1 Percent correct according to serial position in a list of 5 arms in a twelve arm radial maze. The five points on the X-axis represent serial positions 1-5 respectively. Five blocks of 6 sessions are shown. The measure of percent correct was gained by averaging over all subjects across the 6 sessions in a block for a given serial position. Error bars indicate standard errors of the mean scores.

However, during the next block of training (Sessions 25-30), although there was a significant effect of serial position on performance [$F(4,88)=2.96$, $p<0.05$], the data just failed to significantly conform to a quadratic function [$F(1,22)=3.56$, $p=.07$]. Post-hoc comparisons for this block showed that Positions 1, 2 and 5 were all significantly different from position 4 at the $p<0.05$ level. Even though Position 4 was consistently inferior to all the other positions (except to position 3 in Sessions 19-24), as training progressed accuracy at Position 4 increased from 56 percent in Sessions 1-6 to 69 percent in Sessions 25-30. Accuracy at the two extremes (Positions 1 and 5) remained fairly stable once the SPE was established. Therefore, although Part 1 indicated that a 5-arm list presented in a 12-arm maze could result in a SPE, as training progressed it showed signs of weakening. Examination of Figure 2.1 suggests that this occurred because accuracy for middle list positions improved with training.

The emergence of a SPE in Part 1 was similar to the results of DiMattia & Kesner (1984) who used an 8-arm maze, but the present results are a clearer demonstration of a SPE than that observed in most other studies (e.g. DiMattia & Kesner, 1988; Kesner & Beers, 1988; Kesner et al.,1988) which used 8-arm mazes but otherwise similar procedures. One possible reason for the disparity between Dimattia & Kesner (1984) and the results of other studies conducted by Kesner and colleagues is that most of their studies have used a selection criterion of 75 percent accuracy prior to inclusion of a rat in the group average. Thus, as noted by Gaffan (1992), the presence of a SPE may be obscured in many studies because of a ceiling effect. Hence the SPE observed in DiMattia & Kesner (1984) and the present study may have been clearer than seen in many other studies because they were both free of the confounding influence arising from the use of a data selection criterion.

Another possible reason for inconsistency of observing a SPE across the studies conducted by Kesner and colleagues is that there is a critical period during training in which a SPE is present. The subjects in Kesner et al. (1988) received fewer training trials pre-lesion than in DiMattia & Kesner (1984) so perhaps the emergence of the

SPE in DiMattia & Kesner (1984) required a minimum amount of training. Indeed, early on in training DiMattia and Kesner (1984) observed a primacy but no recency effect. Also, the control group in Kesner et al. (1988), despite not initially showing a SPE, did show one after receiving a sham operation and being trained for further trials. However, with further extended training the SPE may weaken. For example, DiMattia & Kesner (1988) failed to show a convincing SPE in their control rats after 120 training trials. Thus a SPE may take a certain amount of training to emerge and then later disappear with continued training with the 8-arm maze SPR procedure as used by Kesner and colleagues. Therefore, despite the present demonstration of a SPE obtained with a list length of 5 showing signs of weakening by 150 trials, the effect itself was relatively persistent compared with previous research.

Part 2

It might be expected that the shift from a 5- to 7-item list would make for an even more difficult task, and hence increase the magnitude of the SPE observed in Part 1. Consistent with this possibility, Part 2 of the experiment demonstrated that the SPE gained with a 7-arm list in the current SPR procedure was more pronounced than that observed with the 5-arm list in Part 1. The first three days training (Sessions 31-33) with the new list length were counted as a period of familiarisation and were not included in the analysis. Figure 2.2 shows accuracy in recognition according to serial position with the new list length. From the 12 sessions of training in Part 2, two blocks of data were obtained. Each data point represents the average percent correct of all 20 rats over 6 sessions of training. For both blocks, accuracy in the middle three positions (3, 4 and 5) was below that of both the first and last positions (1 and 7).

Using a 7-arm list presented in a 12-arm maze in Part 2 resulted in a clear demonstration of the SPE. A one-way ANOVA with serial position as a repeated measure revealed that there was a significant quadratic trend in performance across serial positions for Sessions 34-39, [$F(1,19)=15.95$, $p<0.01$] and Sessions 40-45 [$F(1,19)=23.53$, $p<0.01$]. Post-hoc comparisons for Sessions 34-39 revealed that

accuracy at Position 1 was significantly different from 4 and 5 and that Position 7 was significantly different from 3, 4 and 5 at the $p<0.05$ level. Post-hoc comparisons for Sessions 40-45 revealed continued support for a SPE with both primacy and recency present. Positions 1 and 7 were not significantly different from one another but were both significantly different from Positions 3, 4 and 5 at the $p<0.05$ level. The findings of Part 2 indicated that a 7-arm list resulted in a clear superiority for the first and last list positions and thus a more pronounced SPE than seen with the 5-arm list in Part 1. Although accuracy at the two end positions was not higher in the 7-arm list than the 5-arm list, there was in Part 2 a consistent statistical difference between the two end positions (1 and 7) and the middle three positions. In Part 1, only Position 4 was consistently lower than the two end positions and with continued training this difference gradually decreased. Thus unlike the SPE for the 5-arm list, the poorer performance in the middle of the 7-arm list extended over a greater number of positions.

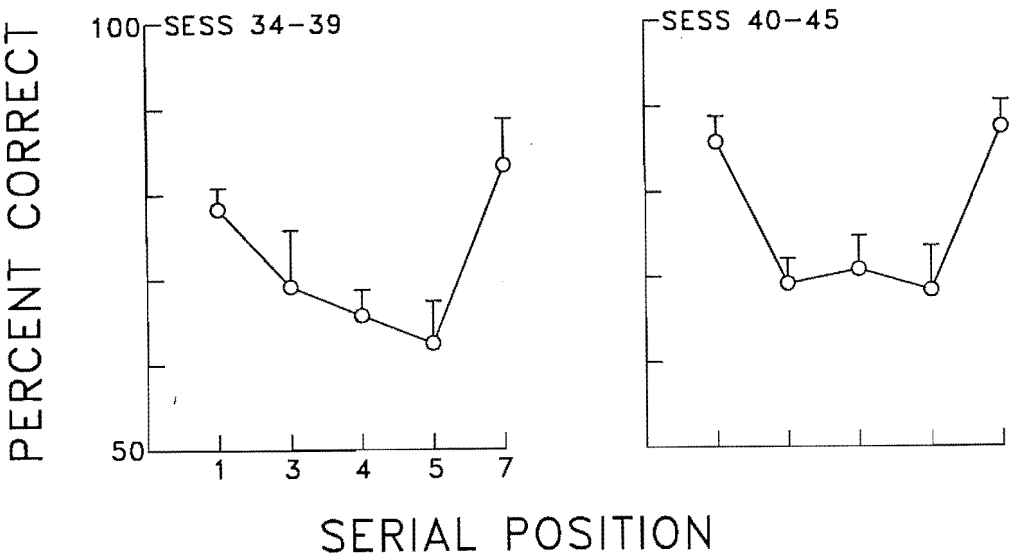

FIG 2.2 Percent correct according to serial position in a list of 7 arms in a 12-arm radial maze. The five points on the X-axis represent serial positions 1, 3, 4, 5, 7 respectively. Two blocks of 6-day sessions are shown. The measure of percent correct was gained by averaging over all subjects across all 6 sessions in a block for a given serial position. Error bars indicate standard errors of the mean scores.

Taken together, the results of both Parts 1 and 2 are a better demonstration of a SPE in rats than has been shown in previous research. There are several differences between the present study and much of the previous research that may have helped the establishment of clear and robust SPEs here. First as discussed earlier, Dimattia & Kesner (1984) and Reed et al. (1991) have suggested that primacy is affected by task difficulty. The present study used a 12-arm maze, which would have made the task more difficult, even when a 5-arm list length was used. Greater task difficulty may arise when using a 12-arm maze because the arms are less spatially separated from one another or because rats cannot successfully adopt a strategy of remembering 'where they had not been'. Second, group size may be important. In Dimattia & Kesner (1988), Kesner & Beers (1988) and Kesner et al's (1988) studies group sizes were very small (n=4-6) compared to the present study (n=20-23) and were slightly smaller than used by Dimattia & Kesner (1984) (n=10).

In Part 2 of the present study it was found that only 12 out of 20 rats (60%) showed an individual SPE. Figure 2.3 shows accuracy according to serial position for each rat in Part 2 summed over all 12 sessions (i.e. 12 trials per data point). Twelve of the 20 rats displayed evidence of superior performance at Positions 1 and 7 over Positions 3,4, and 5. Rats 2, 4, 9, 13, 14, 16, 18, and 20 were not considered to have demonstrated clear primacy and recency effects. Therefore, small groups run a considerable risk of not showing a SPE because of the possibility that the group will contain rats with idiosyncratic biases favouring particular arms. This is especially the case when the number of training trials is limited.

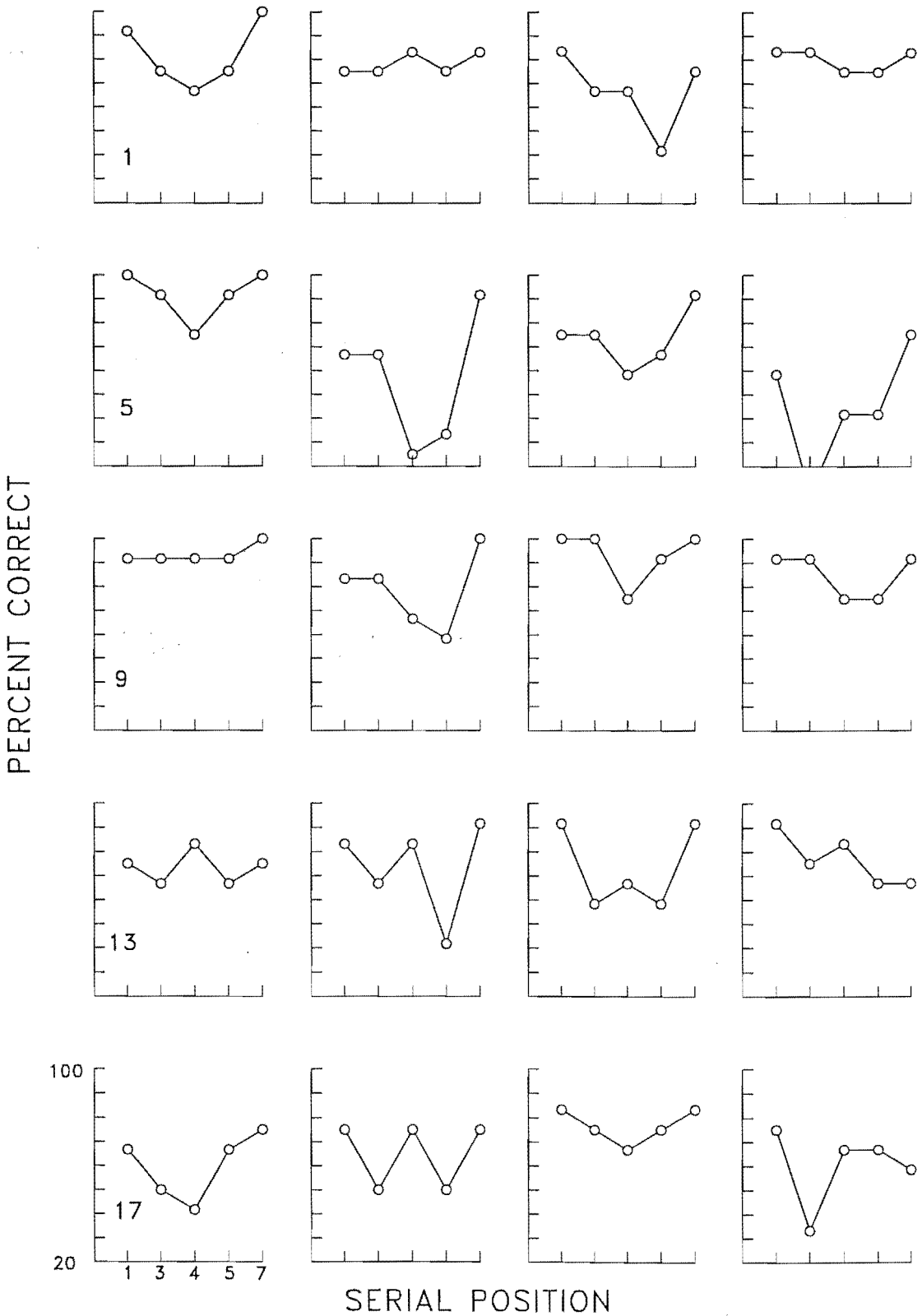

FIG 2.3 Percent correct according to serial position in a list of 7 arms in a 12-arm radial maze for 20 individual rats. The five points on the X-axis represent serial positions 1, 3, 4, 5, 7 respectively. The measure of percent correct was gained by averging performance over all 12 sessions in Part 2 for a given serial position.

A further difference between the present study and earlier studies, which may explain the maintenance of the SPE, is the number of trials conducted in a day. The present study used five trials per day, whereas the studies conducted by Kesner and colleagues used one trial per day. It may be that performance for the last four trials of each day was subject to interference by stimuli presented on earlier trials, despite long intervals between trials. Such proactive interference from prior trials has been observed previously in other maze-based memory tasks (Roberts & Dale, 1981; Grant, 1981). Interference would not be expected in the one-trial-per-day procedure used by Kesner and colleagues, but in the present study it may have counteracted improvement in performance with extended training. Therefore, in the present study the SPE may have been maintained because performance was held below the asymptotic levels observed with continued training in other studies (e.g. DiMattia & Kesner, 1988). If early trials had interfered with performance on subsequent ones, then accuracy would have improved with continued training for the first trial of a session but not for later ones.

The question of whether the order of trials in a session had an effect on accuracy was addressed using a reanalysis of the data from both Parts 1 and 2. Figure 2.4 demonstrates that interference across trials did not influence the development and maintenance of the SPE because no systematic changes in accuracy with continued training occurred as a product of whether the trial was the first, second, third, fourth or fifth of the day.

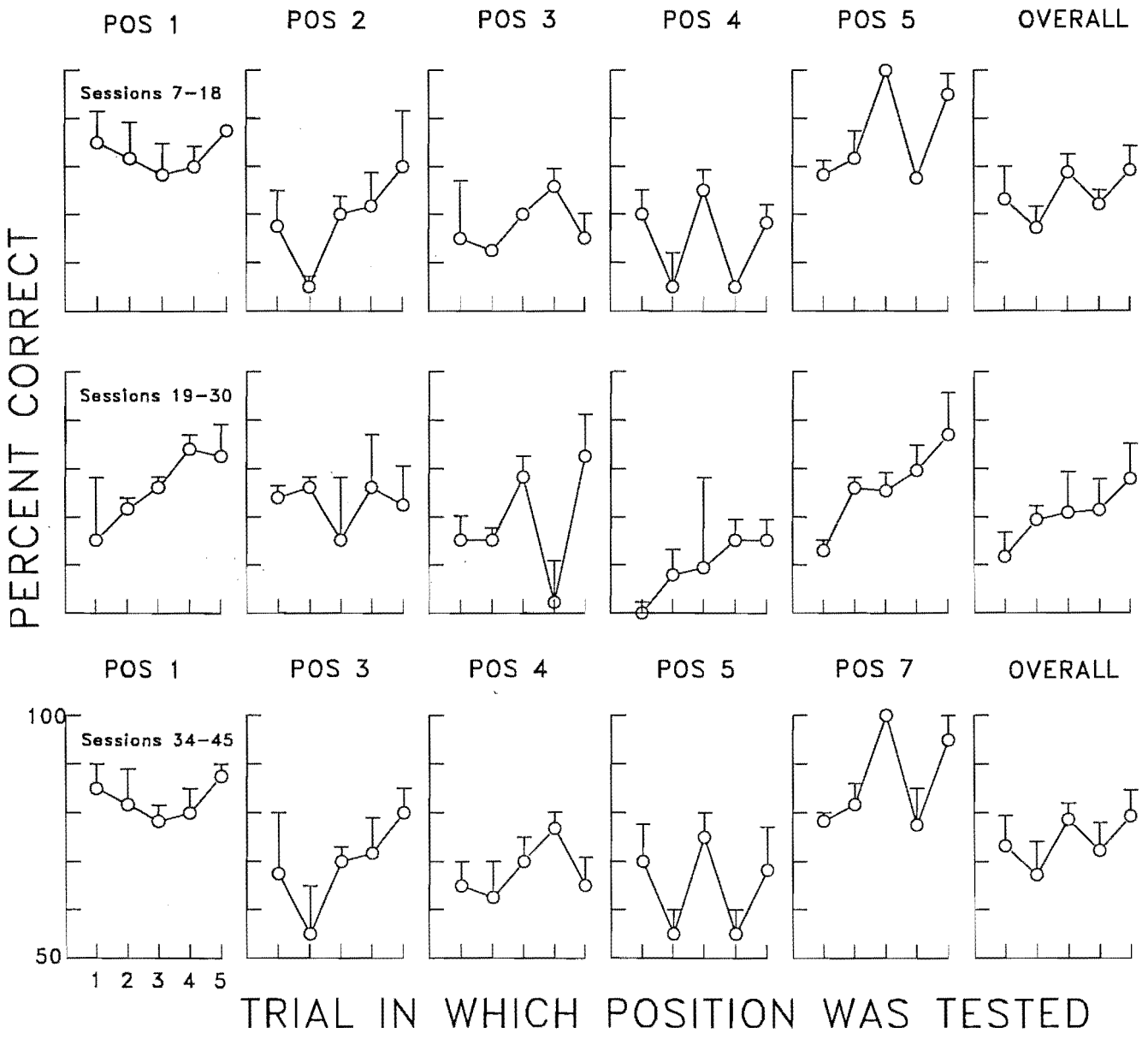

FIG 2.4 Percent correct at a given serial position as a function of the trial number within a session. The 5 points on the X-axis represent trial number 1-5 respectively. Percent correct was gained by averging over all rats from Sessions 7-18 (top row), 19-30 (middle row) and 34-45 (bottom row). The 6 graphs on the top and middle rows are from the data obtained using the 5-arm list in Part 1 and show the effect of trial number on serial positions (1, 2, 3, 4, 5) and the effect over all serial positions combined together. The 6 graphs on the bottom row are from the data obtained using the 7-arm list in Part 2 and show the effect of trial number on serial positions (1, 3, 4, 5, 7) and the effect over all serial positions. Error bars were obtained from the standard errors of the mean scores.

A build-up of proactive interference across trials would be indicated by a systematic decrease in accuracy across trials - however, this was not observed. The top row of Figure 2.4 shows accuracy according to trial of the session for Serial Positions 1, 2, 3, 4, 5 and over all serial positions combined across Sessions 7-18 (i.e. the first 12 sessions in Part 1 in which a serial position effect was present). The second row shows the same data from Sessions 19-30 (Part 1). The third row of graphs is data from Sessions 34-45 (Part 2) and shows accuracy according to trial of the session for Serial Positions 1, 3, 4, 5, 7 and for all serial positions combined overall. During Sessions 7-18 and Sessions 34-45 there were no systematic changes in accuracy at either a given serial position or for all positions combined overall as trials in a session increased. Thus, accuracy was not necessarily greater or less in the fifth trial compared to the first trial of a session. For Sessions 19-30 there was some visual indication that accuracy at Positions 1 and 5 increased as trial in the session increased, as opposed to the expected decrease if there had been a build-up of interference, but these trends failed to reach statistical significance in a 1-way repeated ANOVA for linear trend. Finally, Figure 2.4 shows that there were no systematic changes in accuracy for the first, second, third, fourth or fifth trial as training proceeded across the sessions in Parts 1 and 2. Therefore, within a session and across sessions there were no systematic improvements or impairments in accuracy as a product of the trial order.

Having established that the SPE can be demonstrated in rats using a 7-arm list presented in a 12-arm maze, it remains to be shown that the primacy and recency effects are independent from one another as shown in human memory research. The independence of primacy and recency effects is an important demonstration if we are to examine the potentially differential effects of lesions on these aspects of SPR performance and to draw comparisons to human research. Experiment 2.2 examined whether primacy and recency effects can be altered independently of one another by investigating two manipulations which in several species have been shown to reduce to recency effect but leave primacy intact.

EXPERIMENT 2.2 Effect of Delay and Delay Task on Serial Probe Recognition

Although the basic SPE obtained with a variety of non-human species seems to mirror the SPE obtained with humans (e.g. pigeons and monkeys - Wright et al., 1985; Wright & Watkins, 1987; and rats - DiMattia & Kesner, 1984; Experiment 2.1) there has been little research which has examined the effects of behavioral manipulations on the SPE in animals. The exploration of such manipulations is of interest for several reasons. Firstly, if we wish to compare human and nonhuman studies which relate to the SPE, then we need to be confident that the primacy and recency effects behave similarly across species. Second, if we wish to explore the effects of lesions on the SPE, then it is desirable to establish that the primacy and recency effects can be altered independently of one another, and to develop procedures which can be used to challenge performance and thereby reveal differential lesion effects in terms of a susceptibility to interference.

Human research has identified a number of factors which influence the SPE and thus demonstrate their independence, in particular several manipulations have been shown to alter primacy or recency differentially. Two manipulations which have been shown to disrupt recency but leave primacy relatively unaffected are a delay between list presentation and subsequent recall or recognition (e.g. Postman & Phillips, 1965; Glanzer & Cunitz, 1966; Wright et al., 1985) and the introduction of an interfering task or stimulus between list presentation and recall (e.g. Glanzer, Gianutsos & Dubin, 1969; Gardiner, Thompson & Maskarinec, 1974; Roediger & Crowder, 1975). Glanzer & Cunitz (1966) presented subjects with a 15-word list. With no delay before recall subjects demonstrated both primacy and recency. As delay increased up to 30 s, the recency effect systematically decreased but the primacy effect remained intact. Similarly, Roediger & Crowder (1975) demonstrated that the decrease in recency caused by a 30 s 'rest' period between presentation and recall was made significantly more extreme by requiring subjects to subtract numbers during this delay. Neither the delay in Glanzer & Cunitz (1966) or the delay plus task in Roediger & Crowder (1975)

had an effect on the primacy portion of the SPE. Thus, the recency effect, but not the primacy effect, seems to be greatly influenced by retroactive interference.

Despite the substantial research with humans, the effect of delay and intervening events on the SPE in animals has received only limited attention, therefore the degree to which the primacy and recency effects can be differentially disrupted is largely unknown. With respect to the effect of delay on the SPE, a number of nonhuman species appear to show a similar pattern of change in the SPE as that observed with humans. Wright et al. (1985) demonstrated that in pigeons, monkeys and humans recognition of items late in a 4-item list decreased as delay increased, albeit over different time spans for the three species. However, few studies have investigated the effect of delay on the SPE in rats. In one study, Kesner & Novak (1982) examined the effect of delay on SPR performance not for discrete list arms, but the order in which arms were presented. Rats were exposed to all 8 arms in an 8-arm maze, and were then given a choice between 2 arms (either the 1st and 2nd, 4th and 5th or 7th and 8th arm visited in the sequence) and required to return to the arm presented earliest in the sequence (i.e. 1st, 4th or 7th depending on the pair of arms presented). They examined performance for arm pairs at the beginning, middle and end of the sequence and demonstrated that at a 20 s delay accuracy was higher at the beginning and end compared to the middle. With a 10 min delay accuracy was markedly reduced at the recency end (from around 74 to 45 %) while accuracy at the primacy end was less affected (from around 80 to 65 %). However, the SPE reported by Kesner & Novak (1982) may have been confounded by the possible use of a selection criterion which is indicated by the lower than expected variance in their data (see Gaffan, 1992). In the only study to investigate memory for discrete list items (as per most human research), Bolhuis & van Kampen (1988) presented a list of 5 arms to rats in an 8-arm maze and varied the delay between list presentation and a recognition test. However, the effect of delay on the SPE in their study is uncertain because although accuracy for the final list position tended to decrease as delay increased, at the shortest delay a SPE was not always evident. In some parts of their experiment, performance was not clearly

superior at the two extreme end positions over the middle positions, therefore clear primacy and recency effects were not always originally present. Moreover, the shortest delay used by Bolhuis & van Kampen (1988) and Kesner & Novak (1982) was 30 s and 10 min respectively. Because previous research has indicated that large changes in primacy and recency occur prior to 30 s in a number of species (e.g. Santiago & Wright, 1984; Wright, Santiago & Sands, 1984; Wright et al., 1985), it is important to investigate these short delays in rats.

There has been no previous research with respect to the effect of an intervening task or event between list presentation and subsequent recall or recognition on the SPE in animals. Indirectly, there is evidence to indicate that in many maze-based procedures rats show little susceptibility to the disruptive effects of delay events (i.e. retroactive interference). For example, Maki, Brokofsky & Berg (1979) and Beatty & Shavalia (1980) have found little evidence that rats are impaired in 8-arm maze tasks despite the presence of delays and a variety of events within the delay. However, there is some indication that in the 8-arm maze, it is possible to impair memory performance in rats under certain conditions. For example, Roberts (1981) required rats to run down 1, 2 or 3 other mazes after being exposed to 4 predetermined target arms in an 8-arm maze. After exposure to the other maze(s) the rat was required to return to the 4 originally baited arms and ignore the previously unvisited arms. Roberts found that while a delay of up to 228 s (the average time required to run the 3 other mazes during the delay) did not reduce performance on its own, the greater the number of mazes interpolated into the delay, the greater the reduction in subsequent choice accuracy. Therefore, although it is possible to show a disruption to memory performance with rats using maze-based procedures, the conditions which produce such disruption remain to be fully determined and the effects of such disruption are yet to be investigated using the SPR task.

The above review indicates that particularly with rats, and to some degree with nonhuman species in general, there have been few convincing demonstrations of either

delays or delay tasks producing a decrease in recency but not primacy. Thus, previous research has not demonstrated the independence of the primacy and recency effects in a manner analogous to that observed in humans. Such a demonstration in rats is desirable before examining the effects of lesions in Experiment 2.3 if we wish to integrate the lesion effects with the existing human data. Therefore, Part 1 of the present study examined the effect of delays up to 60 s on the SPE obtained in rats using the same basic 7-arm list procedure as used in Part 2 of Experiment 1. Part 2 of the present study investigated whether giving rats free access to food reinforcement during the delay resulted in an impairment to recency but not primacy, as has been demonstrated in humans when they are presented with a number of stimuli during a short delay (e.g. Glanzer et al., 1969; Gardiner, et al., 1974; Roediger & Crowder, 1975). Free access to food was chosen as the potentially disruptive event because previous research with pigeons responding on a DMTS task has shown this to be an effective disruptor (Jans & Catania, 1980).

METHOD

Subjects and *Apparatus*

Subjects and apparatus were the same as in Experiment 2.1.

Procedure

The same basic SPR procedure that was used in Part 2 of Experiment 2.1 was used in the present experiment. That is, each trial of training involved two phases - a presentation phase in which a sequence of successively available arms was presented to the subject followed by a test phase in which recognition for one of the list arms was examined. Again only serial positions 1, 3, 4, 5 and 7 were tested for recognition. However, a difference from the previous study was that 6 <u>new</u> sequences of arms were chosen. These predetermined 7-arm sequences are shown in Table 2.1.

TABLE 2.1 The arm sequences used in Part 3. Each number represents an arm on the maze. All twelve arms are used but only arms 1, 3, 5, 7, 9, 11 appear in positions one, four, and seven; and only arms 2, 4, 6, 8, 10, 12 appear in positions two, three, five, and six. Hence, positions one, four, and seven are comparable in that the same arms are presented in each. Likewise for positions three and five. Numbers in brackets are the comparison arms shown with the list arm during the test phase. Positions two and six have no comparison arm because they were not tested.

Sequence	Serial position						
	one	two	three	four	five	six	seven
A	3 (1)	10	2 (4)	5 (7)	8 (6)	12	9 (11)
B	5 (7)	2	8 (6)	11 (9)	12 (10)	4	1 (3)
C	11 (9)	6	10 (12)	3 (1)	2 (4)	8	5 (7)
D	1 (3)	8	4 (2)	7 (5)	10 (12)	6	11 (9)
E	7 (5)	12	6 (8)	9 (11)	4 (2)	10	3 (1)
F	9 (11)	4	12 (10)	1 (3)	6 (8)	2	7 (5)

These new sequences were generated under the same rules that governed production of earlier lists, but in addition (for reasons to do with data analysis - see Results and Discussion section) had to be capable of allowing the calculation of a bias-free measure of accuracy (*Log d*) between arm pairs. In this procedure each arm had to be presented with only one other arm (i.e. Arm 1 was paired with Arm 3, 2 with 4, 5 with 7, 6 with 8, 9 with 11 and 10 with 12). On half the trials (involving a particular stimulus pair) one of the arms was presented in the list and the other arm not; when tested for recognition both arms in the pair were presented simultaneously and the rat chose between them. On the other half of the trials (involving the stimulus pair), the alternate arm in the pair was presented in the list. Such pairing of arms makes it possible to generate the stimulus-response matrix in Figure 1.9, which in turn allows for a calculation bias-free accuracy (*Log d* - see Section 1.3.2). The *Log d* calculated in this manner is an average of the *Log d*s for individual pairs of arms that are tested at a particular serial position. For example, at Position 1, the *Log d* calculated is an average of the individual *Log d*s for arm pairs 1 and 3, 5 and 7, 9 and 11. It should also be

noted that the usual calculation of *Log d* is for individual data, and therefore is free of idiosyncratic response biases exhibited by a single subject. However, the measure of *Log d* obtained using the current procedure is free from any consistent response bias demonstrated by the group as a whole.

Part 1 examined the effect of delay of choice on the SPE in rats. Whereas in Experiment 2.1 the delay between list presentation was fixed at approximately 5 s, in Part 1 of the present experiment this delay was varied. Following training in Experiment 2.1 rats were run for a further 12 sessions using the sequences in Table 2.1 and a delay of 5 s, this data was not included in the present analysis. Following this period of training, rats were exposed to each of the 5 delay conditions (5, 10, 20, 30 and 60 s) over the period of 5 sessions (one delay per session). This preliminary training was to familiarise the rats with the imposition of a delay between list presentation and test phases and the data from these 5 familiarisation sessions was also not used in the subsequent analysis. Following familiarisation, the 5 delay conditions were repeated for 6 times each in a random order over the next 30 sessions with all rats receiving the same delay in a given session.

Part 2 examined the disrupting effect of providing free access to chocolate during a fixed 10 s delay period between sample presentation and the recognition test phase of trials. On every alternate session, a 100 ml cup full of chocolate chips was lowered into the middle of the central platform of the maze. The rats were free to feed from the cup until the 10 s delay ended, then the cup was raised at the same time as the 2 doors to the comparison arms were raised. On every other session, free access to chocolate was not available during the 10 s delay. The rats were trained for 12 sessions in this condition, that is, 6 sessions when chocolate was available in the delay and 6 alternate sessions when it was not.

RESULTS and DISCUSSION

The results from Parts 1 and 2 are presented in separate sections below.

Part 1

Of interest in Part 1 was whether the SPE obtained in rats with a 7-arm list presented in a 12-arm maze was altered by imposing delays between list presentation and subsequent recognition. Specifically, does recency decrease with increasing delay (up to 60 s) but primacy remain relatively intact, as is the case in humans and a number of other species? The results demonstrated that both the primacy and recency effects obtained with rats in a 12-arm maze, using a 7-arm list, were reduced by imposing a delay between list presentation and recognition. However, accuracy in Positions 1 and 7 decreased in a differential manner. Accuracy at Position 7 (recency) decreased systematically as delays increased, but accuracy at Position 1 (primacy) was largely unaltered by delays up to 30 s and then dramatically decreased between 30 and 60 s.

Figure 2.5 shows the effect of varying the length of delays on the SPE. Percent accuracy is given for Positions 1, 3, 4, 5 and 7 at each of the five delays. Each data point represents the average score of 20 rats from the 6 sessions of training conducted at a given delay. The SPE observed with a 7-arm list at a 5 s delay in Experiment 2.1 was also observed in the current experiment (open circles in Fig. 2.5). The existence of a SPE (with both primacy and recency present) at this delay was confirmed by the presence of a significant quadratic function in accuracy across serial positions [$F(1,19)=11.08$, $p<.01$].

As delays increased over the range 5-30 s, the recency effect became progressively weaker while the primacy effect remained approximately the same, but the primacy effect was removed entirely at the 60 s delay. Analyses of variance showed that there was a main effect of delay on accuracy [$F(4,76)=5.74$, $p < .001$], a main effect of serial position on accuracy [$F(4,76)=8.10$, $p < .001$], and a significant

interaction between a quadratic function in the data (across serial positions) and delay [F(4,76)=2.52, p<.05]. Figure 2.5 indicates a difference between serial positions in that accuracy at Positions 1 and 7 decreased, whereas accuracy in the three middle positions did not. This observation was confirmed by analysing the effect of delay on accuracy for each serial position separately; the effect of delay was significant only for Positions 1 [F (4,76) = 6.98, p < .001] and 7 [F (4,76) = 3.60, p < .01]. Furthermore, although a significant (p<.01) quadratic trend was present in the data at 5, 10 and 30 s (and almost at 20 s - F=3.52, p=.07), at the 60 s delay there was no significant quadratic or linear trend in accuracy across serial positions (F<.01). Thus, increasing delays affected the shape of the SPE function.

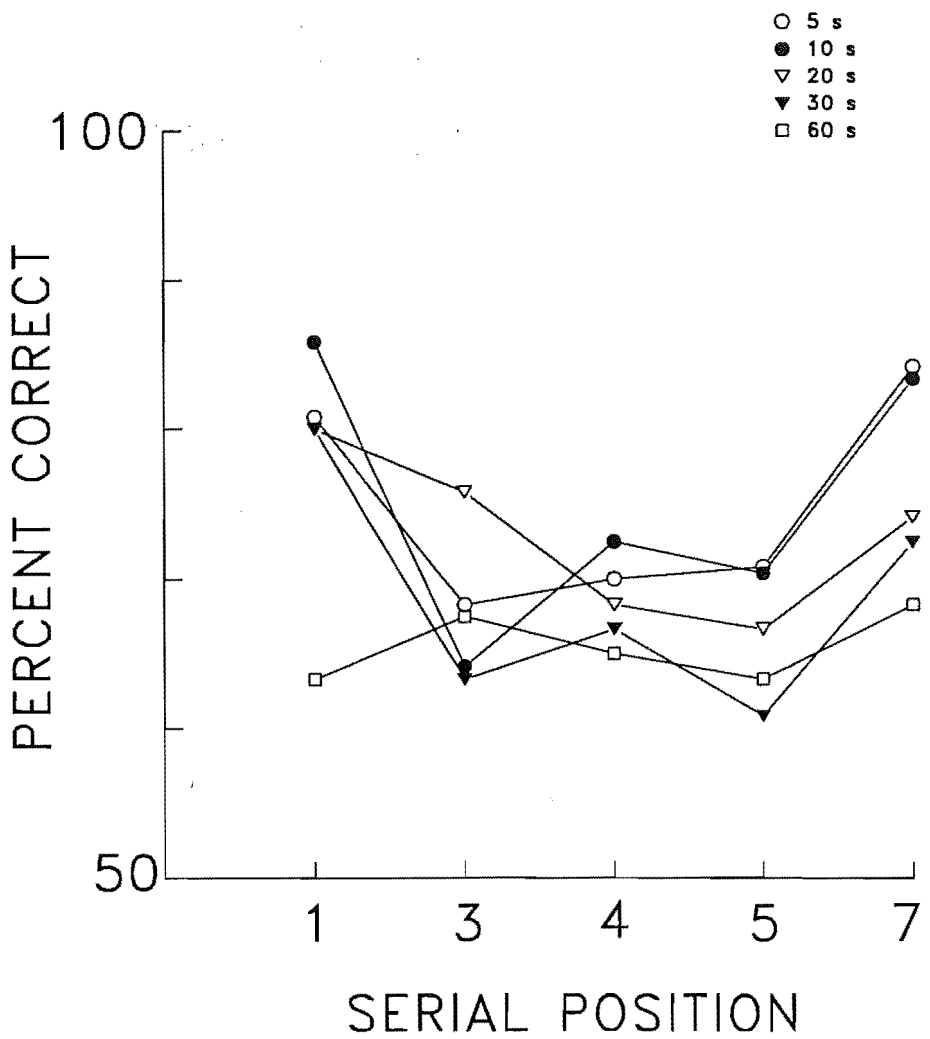

FIG 2.5 Percent correct according to serial position in a list of 7 arms in a 12-arm radial maze. The five points on the X- axis represent serial positions 1, 3, 4, 5, and 7 respectively. The Y-axis gives percent correct, gained by averaging over all 20 subjects across all 6 sessions for a given serial position. Open circles, closed circles, open triangles, closed triangles and open squares show performance in the 6 sessions conducted at each delay of 5, 10, 20, 30 and 60 s, respectively.

Figure 2.5 indicated that although accuracy at both Positions 1 and 7 was reduced, the pattern of decay in accuracy with increasing delays was different. Accuracy at Position 7 decreased at the shorter delays, whereas accuracy in Position 1 did not decrease noticeably until the 60 s delay. Post-hoc comparisons of the percent correct scores at Position 1 showed that accuracy at a delay of 60 s was significantly different (at $p<.05$) from accuracy at all other delays, but earlier delays were not different from one another. Whereas, at Position 7, percent correct at the shortest (5 s) delay was significantly different from accuracy at 20, 30 and 60 s delays, and accuracy at the 10 s delay was significantly different from accuracy at the 30 and 60 s of delay. There were no other significant accuracy differences between delays at Position 7.

Given that accuracy at both Position 1 and 7 appear to decrease in a different manner, an informative analysis is to quantify the effect of delay on recognition for items at various positions in the list. For this analysis, two quantitative models for memory decay were used; the exponential model (White & McKenzie, 1982) and the hyperbolic model (McCarthy, 1981). Both of these models express performance in terms of changes to *Log d* (thus it was necessary to choose arm sequences that would allow for the calculation of *Log d* at each delay - see Table 2..1). A great deal of research has shown that *Log d* decays with increases in delay between stimulus presentation and subsequent recognition in a manner well described by both exponential and hyperbolic functions. (see McCarthy & White, 1987 for a review). Because both models are of potential value and there was no basis to choose one over another to describe the present data both were examined here.

The exponential model is given in Equation 1 (Section 1.3.2), which states that accuracy decays exponentially from an initial level (*Log do*) at a rate quantified by the fitted parameter *b*. The greater the value of *b*, the greater the rate of forgetting. The hyperbolic model is characterised by Equation 2 (Section 1.3.2), which states that accuracy decays hyperbolically from an initial level (*Log do*) at a rate quantified by the fitted parameter *h*. The lower the value of *h*, the greater the rate of forgetting. In both

equations initial accuracy, *Log do*, reflects performance accuracy independent of reductions due to delay and may be affected, for example, by the number of arms in the apparatus. The values of *b* and *h* depend on characteristics of the memory process involved.

Figure 2.6 shows the effect of delay on accuracy measured using *Log d*. *Log d* was calculated by assigning correct and error responses of all 20 rats for each delay and serial position to the matrix in Figure 1.9. In Figure 2.6, the top, middle and bottom panels show changes in *Log d* as a function of delay for Positions 1, 4 and 7 respectively. Only data from Positions 1, 4 and 7 were presented because performance at these three positions was studied using the same stimulus-arm pairs, whereas performance at Positions 3 and 5 was studied using other arms. The graphs on the left and right are fits of the exponential and hyperbolic functions respectively, to the values of *Log d* obtained. The curves in Figure 2.6 were fitted to data using nonlinear regression, which provided empirical estimates for the free parameters *Log d* and *b* or *h*. On each curve the measure of performance extrapolated to the 0 s delay (*Log do*) is the intercept of the curve at the vertical axis.

The exponential and hyperbolic models provided reasonably good descriptions of the changes in *Log d* as a function of delay, although they fitted the data from later serial positions better than earlier ones. Both models showed that the decay rate (characterised by the *b* and *h* parameters) was greatest for Position 7, intermediate for Position 1, and least for Position 4. Also, there was no difference in ability to recognize stimuli at a 0 s delay (characterised by the *Log do* parameter in both models) between Positions 1 and 7, which both showed greater *Log do* values than obtained at Position 4. These results indicate that at the middle list position, accuracy would be poor even at the 0 s delay; but there is very little decay in memory for list items. Of more interest is the comparison of Positions 1 and 7 given that a number of species demonstrate a decrease in recency but an intact primacy as delay increases. The analysis demonstrated that although accuracy extrapolated back to the 0 s delay is comparable

in the two positions, memory for a list item decays more quickly and systematically at Position 7 (the recency end) than at Position 1 (the primacy end).

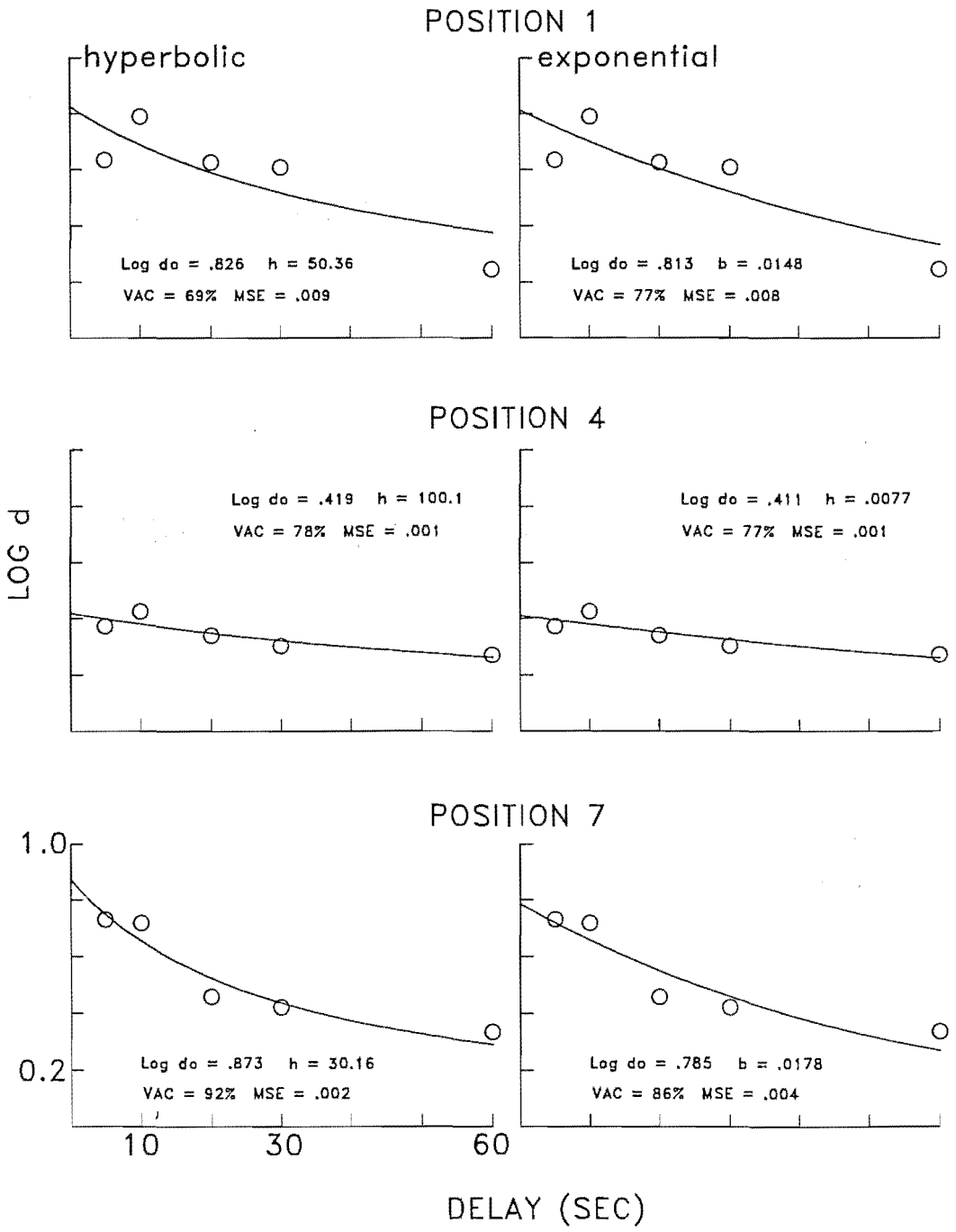

FIG 2.6 Point estimates of stimulus discriminability *Log d* as a function of delay *t* for list positions 1, 4 and 7 in Part 1. Graphs on the right and left are from fits of the exponential and hyperbolic decay models respectively. Nonlinear least squares fits to the negative-exponential and rectangular-hyperbolic decay models are shown as solid lines. Also shown for each list position are the values of the decay in accuracy (*b* and *h*), the predicted values of initial discriminability (*Log do*), the variance accounted for (VAC) and mean square error (MSE) of the estimates.

The observed decrease in recency as delay increased with rats was the same as that found in other species including humans using a variety of list stimuli and procedures (e.g. Postman & Phillips, 1965; Glanzer & Cunitz, 1966; Wright et al., 1985). Further, the present demonstration of the effect of delay on recency was clearer than previously shown with rats in the studies by Bolhuis & van Kampen (1988) and Kesner & Novak (1982). However, a difference in the results of this study and earlier research with other species is that although primacy was left intact at the shorter delays, at the longest delay accuracy for Position 1 fell to the same level as other serial positions.

The reason why primacy decreased between 30 and 60 s in the present study is unclear. It may be that because on most trials rats were left in the maze for 30 s or less, the presence of a relatively long 60 s delay resulted in a confusion as to whether they were still in the same trial or about to begin a new one. That is, at the end of a 60 s delay the test phase was treated as a new presentation phase and the rat went to the first door it saw. However, this explanation seems unlikely because accuracy levels would be expected to fall to 50% on average at all serial positions under such a strategy by the rats, not just Position 1, and Figure 2.5 shows that this was not the case and that performance never fell below 60%.

The SPE itself and alterations in accuracy observed across delays were not the spurious product of the major design faults noted by Gaffan (1992) and Gaffan & Gaffan (1992). These authors have claimed that low between-subject variability in the data may indicate a non-independence of trials arising from stimulus selection procedures which allow for stimulus preferences across a group to influence accuracy, or from experimenter biases. However, the arm sequences used in the present research excluded the possibility that a group bias influenced the shape of the SPE because the same stimuli were used equally often as correct and incorrect stimuli across a range of serial positions. Indeed, a X^2 analysis (as suggested by Gaffan, 1992) to compare the observed variance in data obtained at each delay against that

expected from a binomial distribution showed that the variance in the current data did not deviate significantly. Specifically of the 25 cases, across all 5 serial positions at all 5 delays, only 3 of the ratios of expected versus observed variances lay outside the 99% confidence interval (see Gaffan, 1992 for a description of this analysis). Thus, although the reasons for the decrease in primacy between 30 and 60 s delay is not clear, this decrease did not appear to be the result of any influence extraneous to the delays themselves.

Although it was expected that the primacy effect would remain virtually unaltered following a delay, there is already some evidence which has indicated that not only recency effects but also primacy effects may be reduced, albeit differentially, in maze-based SPR tasks. Kesner & Novak (1982) also introduced delays before recognition in the task requiring memory for list-arm order described earlier. Their results indicated that there was some reduction in primacy with their procedure at a 10 min delay. Furthermore, the amount of decrease exhibited by their primacy effect (approximately 85 to 65 %) is comparable to the absolute change exhibited in the present experiment (81 to 63 %). Given that Kesner & Novak's shortest delay was 10 min, it may have been the case that the reductions observed by them would have also taken place at much shorter delays. What the present experiment demonstrated was that although both primacy and recency may decrease with increasing delays, it is the manner in which they decrease that is different. That is, the recency effect is reduced at short delays (10-30 s), whereas the primacy effect remains largely intact until longer delays (30-60 s). Thus to a large degree, the presence of a delay between list presentation and subsequent recognition has a differential effect on primacy and recency effects.

Part 2

Part 2 examined the effect of free access to chocolate during a 10 s delay between stimulus presentation and the recognition test. The results showed that the presentation of a potentially disrupting event (free food) during a short delay decreased recognition for arms in the recency portion of the list. Figure 2.7 shows data obtained

from the 12 sessions of training in Part 2; a baseline 'no delay-chocolate' condition of 6 sessions (open circles) in which a 10 s delay was imposed between list presentation and the recognition test, and the 6 interpolated sessions in which chocolate was made available during the 10 s delay (filled circles). Each data point represents the average percent correct of the 20 rats from the 6 sessions of training.

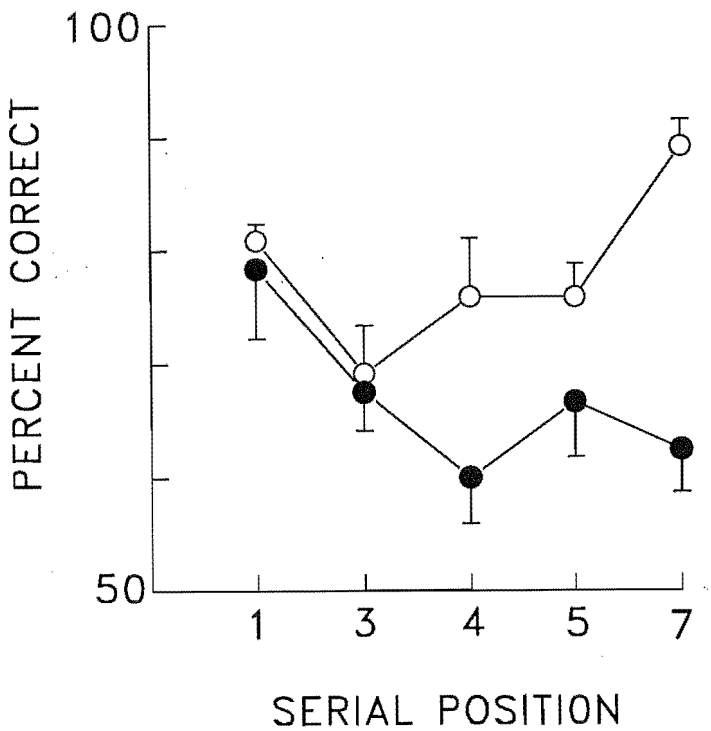

FIG 2.7 Percent correct according to serial position in a list of 7 arms in a 12-arm radial maze in Part 2. The five points on the X-axis represent serial positions 1, 3, 4, 5, 7 respectively. The Y-axis gives percent correct, gained by averaging over all 20 subjects across all 6 sessions at a given serial position. Unfilled circles are data obtained from the 6 sessions in which there was a delay of 10 s between list presentation and subsequent recognition. Filled circles are data obtained from the 6 sessions in which free access to chocolate was made available during the 10 s delay. Error bars indicate the standard errors of each mean score.

Figure 2.7 indicates that memory for arms late in the list was more greatly disrupted by free access to chocolate than memory at early serial positions. A 2-way ANOVA with Condition (Chocolate versus No Chocolate in delay) and Serial Position as repeated measures revealed a significant effect of Condition [$F(1,19)=14.99$, $p < .001$], Serial Position [$F(4,76)=4.07$, $p < .01$] and a significant interaction between Condition and Serial Position [$F(4,76)=2.81$, $p < .05$]. Post-hoc comparisons of the effect of condition on accuracy at each serial position separately showed that only Positions 4 ($p < .05$) and 7 ($p < .001$) were significantly decreased by introduction of chocolate during the delay. However, Position 7 decreased by the greatest proportion of its baseline, no chocolate in the delay, level. This change in performance at later serial positions as a consequence of condition is characterised by the presence of a significant quadratic trend in percent correct for the baseline condition [$F(1,19)=15.04$, $p < .01$]. However, during free access to chocolate in the delay, there was no quadratic trend in percent correct ($F=2.19$, $p=.15$) and instead there was a significant negative-linear trend [$F(1,19)=7.41$, $p < .05$]. Therefore, the serial positions most greatly disrupted by delays up to 30 s and as a result of free access to chocolate in a 10 s delay were from the recency end of the curve, in particular Position 7. However, unlike the 60 s delay in Part 1, free access to chocolate did not result in the reductions in accuracy observed at Position 1.

Part 2 of the present work demonstrated that inserting a disrupting event in a short delay between list presentation and recognition had a disruptive effect on recency but not primacy. The effects of delay event, as with the effects of delays themselves in Part 1, were largely similar to the patterns observed in human experiments. Human research has typically used procedures which require subjects to perform an arithmetic or verbal task in the delay (e.g. Glanzer et al., 1969; Gardiner et al., 1974; Roediger & Crowder, 1975). The task used here was different from that in human research in that rather than 'requiring' the rat to perform a task, disruption of behavior was achieved by taking advantage of the rats' food deprived state. Despite this difference the effect on recency was the same. It may be the case that imposing any change on ongoing

behavior during the delay will decrease recency, though what counts as ongoing behavior will alter depending on the specific task being employed. For example, requiring human subjects to perform a concurrent task during presentation of a list, and then continuing that concurrent task during a delay results in an intact recency effect, called the 'long-term recency effect' (Bjork & Whitten, 1974; Koppenaal & Glanzer, 1990). However, altering the concurrent task to another task during the delay has the effect of removing recency, leaving primacy intact (Koppenaal & Glanzer, 1990). As with procedures that do not use a concurrent distractor task, it is the alteration of procedure between list presentation and delay, and hence alteration to a subjects' ongoing behavior that has the disruptive effect on recency.

Both the current experiment and Experiment 2.1 were necessary prior to examining lesion effects on the SPE in rats. Experiment 2.1 demonstrated that clear and robust primacy and recency effects could be established in rats. Experiment 2.2 expanded upon the findings of this first study by showing that, in both Parts 1 and 2, primacy and recency effects can be manipulated independent of one another in a manner largely analogous to that observed with humans. This demonstration of a similarity between animal and human SPEs is an important step in drawing together traditionally separate research traditions, and thus it is possible to be reasonably confident about integrating the existing human data with the subsequent study of lesion effects in rat-SPR performance. The introduction of delays in each SPR trial turns the task into a DMTS task with list items as stimuli. As discussed in Chapter 1, DMTS and list-memory performance is disrupted in AD, KS and in subjects administered scopolamine. As suggested in Sections 1.2.3 and 1.3.1, it may be that disruption to the cholinergic input to the HF from the MS is partially responsible for such memory impairments. Thus, rats with MS damage (but perhaps not MB because it is not part of the cholinergic input to the HF) will not only be impaired in SPR performance but also will be relatively more susceptible to the introduction of delays into the task. Another possible implication of the human clinical and experimental data is that MS damage will result in rats being more susceptible to the retroactive interference effects of delay events such as free-

food in the delay portion of a SPR task. Therefore, the procedures developed in Experiment 2.2 were of potential value in not only demonstrating that the SPE in rats is analogous to that in humans, but also that the SPR task can incorporate manipulations which will allow a number of comparisons to be made between MS or MB lesion effects and data from other lines of research which implicate these brain regions in memory. Unfortunately as will be seen in Experiment 2.3, the effects of MS and MB lesions on the basic SPR task without delays or interference presence were sufficiently disruptive to performance to render such manipulation uninformative, thus they were not examined in lesioned rats.

EXPERIMENT 2.3 The Effect of Medial Septum and Mammillary Body Lesions on Serial Probe Recognition

An important line of research in the neurosciences has examined the effect of specific brain lesions in rats using memory tasks which are analogous to those used with human subjects. An established procedure used with rats in this context is the SPR task, which allows an examination of memory for a list of items (see Kesner, 1988 a,b). Experiments 2.1 and 2.2 established that using a SPR task in a 12-arm maze, rats display a robust SPE which is analogous to that observed with humans. That is, like humans, rats show superior recognition for items at the beginning (primacy) and end (recency) versus the middle of the list. This primacy effect is reduced or absent in humans suffering from the neurodegenerative disorders of AD or KS (Gibson, 1981; Adelstein et al.,1992; Baddeley & Warrington, 1970) and previous research has implied that damage to two brain structures connected to the HF (the MS and MB) may underlie this and other memory disruptions in AD and/or KS. Likewise, previous animal lesion research has also implied that these two brain regions may be important for performance in a variety of memory tasks. Therefore the present study investigated the effects of MS or MB damage on memory for list items in the SPR task with rats, in an attempt to further integrate the separate lines of research implicating these brain regions in memory.

Of particular interest in the present study was whether the severe disruption to the primacy component of the SPE, observed in previous human clinical and experimental studies, could be modelled in rats by lesioning the MS. Because basal forebrain damage in the MS (Arendt et al., 1983) and a subsequent loss of acetylcholine activity in the HF (Antuono et al., 1980) are overlapping areas of the neuropathology in AD and KS it may be that damage to the MS underlies the loss of the primacy effect in both AD and KS. Consistent with this view are the findings of studies which have pharmacologically reduced cholinergic activity and subsequently observed a loss of

primacy, but retention of recency, in a manner analogous to that seen in AD and KS subjects (e.g. Crow & Grove-White, 1973; Frith et al., 1984).

There is already some existing evidence that SPR performance is disrupted and that primacy may be more disrupted than recency by MS lesions in rats. Kesner et al. (1988) examined the effect of MS lesions on memory for a list of 5 arms presented in an 8-arm radial maze. Six rats with a relatively larger MS lesion displayed an impairment in recognition accuracy at all serial positions in the list of 5 arms. Four other rats, that were found to have a relatively smaller MS lesion, showed no significant impairment at the final list position but were significantly impaired at all earlier positions. That is, rats with small MS lesions were similar to people with AD and KS in that performance for early and middle positions of the list was more impaired than that for the final position(s).

However as noted in Section 1.3.1, the conclusions of Kesner et al's (1988) study are weakened by the observation that neither the control group or the MS group displayed clear primacy and recency effects prior to surgery. Such problems can be avoided by using the SPR procedure developed in Experiments 2.1 and 2.2. These studies indicated that with a 7-arm list presented in a 12-arm maze, robust and persistent primacy and recency effects do emerge in rats. Therefore, Experiment 2.1 used the current SPR procedure in order to assess whether primacy is indeed more greatly reduced relative to recency when the MS is lesioned.

In addition to the MS lesion, the present study also examined the effect of a MB lesion on primacy and recency effects in rats. The MB are often found to be damaged in people with KS (Victor et al., 1971; Mair et al., 1979; Mayes et al., 1988), and thus implicated in the memory impairments observed in this disorder. The MB have not, however been implicated in the neuropathology or behavioral disruptions observed in AD. Nor do the MB form part of the cholinergic input to the HF. Therefore, the case for claiming that a disruption to normal MS function (and consequent disruption to

hippocampal acetylcholine) is responsible for the similar behavioral disruptions in KS, AD and in subjects given scopolamine would be strengthened by observing a different pattern of disruption following a MB lesion as opposed to a MS lesion. Similarly, given that both the MS and MB are implicated in memory as well as being connected to one another and the HF, the respective roles they play in memory function is of interest. Therefore, the present study examined the effect of a MB lesion on primacy and recency effects and compared the pattern of deficit to that observed with a MS lesion.

A second issue addressed here was the robustness of changes to the SPE in both MS and MB lesion groups. This is an important question to address if we are to determine whether the behavioral deficits following lesions are relatively permanent, as they are in human neurodegenerative disorders, or whether they are transient in nature. Transient lesion effects are problematic because it becomes very difficult to draw definite conclusions about brain region function. For example, a memory deficit may arise because of a general brain insult rather than cellular damage in the area per se. It is not known how responsive lesion effects are to extended training and changes in various aspects of the SPR task.

Two means of assessing the robustness of the lesion effects were examined in the present study. The first means was by training for an extended period of time post-surgery. It may be that the observation of a memory disruption is limited to only a relatively restricted number of training trials before behavior recovers. In previous research, performance has only been examined over a small number of training trials when assessing the effect of lesions on memory for list items. For instance, Kesner et al. (1988) examined performance for 40 trials (8 per serial position) post-surgery, but the longer term aspects of performance were not assessed with training beyond this point. The present study examined behavior over 120 trials (24 per serial position) post lesion for MS rats and over 90 trials (18 sessions) post lesion for MB rats. The second way in which the robustness of memory deficits was examined was by increasing the time for which a rat was exposed to list arms during presentation. Research with

humans has shown that increasing the exposure time to list items increases accuracy for items occurring at the beginning and middle of a list (Murdock, 1962). Therefore, extended exposure to list arms may aid the recognition of those arms, and thereby counteract any reductions in accuracy caused by the lesions, particularly at positions early in the list. For 6 sessions, MS and MB lesioned rats were exposed to list arms for a longer period during presentation to test whether lesion effects were robust with extended exposure.

METHOD

Subjects and *Apparatus*

Subjects and apparatus were the same as in Experiments 2.1 and 2.2.

Procedure

The same basic SPR procedure as used in Experiment 2.1 (Part 2) was used here to examine memory for list items. That is each rat was presented with 5 trials per session in which each trial tested recognition of a list arm at a different serial position (either 1, 3, 4, 5 or 7). Each trial involved two phases - a presentation phase in which a sequence of successively available arms was presented to the subject followed by a test phase (10 s later) in which recognition for one of the list arms was examined. The sequences of arms used were the same as shown on Table 2.1 (see Experiment 2.2).

In order to maximize the use of the 20 subjects, 10 subjects served first as the sham-control group and then later as the MB group. The current research began by examining the effect of a small medial septal lesion on the serial position curve in rats. (A small lesion was chosen because of the indications from Kesner et al., 1988, that relatively large lesions are extremely disruptive to overall performance). Training began with all 20 rats being run for 6 sessions (30 trials) in a baseline condition. Following completion of the baseline training the rats were assigned to either a sham-operation control group (n=10) or to the MS group (n=10) such that the serial position

curves exhibited by each group prior to lesions were similar. Animals were allowed 5 to 7 days to recover post-surgery and then they were given the same behavioral procedure used before surgery. Individuals from the two groups were tested in a mixed order. Following surgery the rats in the MS group were tested for 4 blocks of 6 sessions per block (120 trials). The rats in the sham-operated control group were tested for 3 blocks of 6 sessions per block (90 trials) post-surgery before receiving a MB lesion. After being given a MB lesion the rats were allowed 5 to 7 days to recover and then they were given the same behavioral procedure used before surgery. The 6 rats that survived MB lesion surgery were trained for 3 blocks of 6 sessions per block (90 trials).

Following the 4th and 3rd blocks of training post-surgery for the MS and MB groups respectively, the effect of increasing the exposure time to list arms was examined. Exposure to list arms was increased by requiring the rat to spend a longer period of time down each arm during presentation, achieved by placing more chocolate at the end of a list arm. The procedure was the same as previously except that on every alternate session 3 pieces of chocolate were placed at the end of each list arm in the presentation phase of a trial. On every other session only 1 piece of chocolate was placed at the end of each list arm as was the case with previous baseline training. The rats were run for 6 sessions for each of these conditions. The MB, but not the MS rats, were then trained for a further 6 sessions in the basic baseline procedure with only 1 piece of chocolate per arm in the presentation phase.

Surgery

Before examining the effect of lesions on memory tasks in the present research, an attempt was made to develop the techniques to lesion the MS using Ibotenic and Quisqualic acid. The advantage of these neurotoxins is that they are relatively specific to the brain region being lesioned and thus leave surrounding tissue and fibres of passage undamaged (Dunnett, Whishaw, Jones & Bunch, 1987). Thirty five operations were conducted primarily with Quisqualic acid (but also some with Ibotenic acid) in both

the NBM and MS regions, using a variety of different solution mediums, at a variety of dose levels and in single or multiple stage surgical sessions. Unfortunately, the procedures were never refined to a successful degree. Two general outcomes were the result of neurotoxic surgery - either a rat would survive surgery, but histological analysis would reveal that there was only very slight cell damage; or the rat would fail to survive past 24 hours. Eventually, it was decided to use radiofrequency lesions. Preliminary work using this means revealed quite precise control over lesion site and size as well as high survival rates.

Radiofrequency MS and MB lesions were made using a Radionics RFG-4A lesion generator with a 0.25 mm electrode lowered to the appropriate co-ordinates in the brain. Rats were anaesthetized with an i.p. injection of a xylazine (50 mg/kg) / ketamine (100 mg/kg) mixture. The rat was then placed in a stereotaxic apparatus with the incisor bar set at 3 mm below the interaural line. The MS lesion was made at the midline, 0.8 mm anterior to bregma and 5.0 & 5.8 mm below the dura. For the dorsal site, the temperature was raised to 60^{o} C for 1 minute. For the ventral site, the temperature was raised to 65^{o} C for 1 minute. For the sham-operated control group, the electrode was lowered into the cortex above the MS but no current was passed. After a period of training, the sham group received a MB lesion at 2.6 mm anterior to lambda, +/- 0.5 mm lateral to the midline and 9 mm below the dura. At each site the electrode temperature was raised to 65^{o} C for 1 minute.

RESULTS

A reconstruction of the largest and smallest lesions in both the MB and MS lesion groups is shown in Appendix A. The histological analyses indicated that all subjects in the MS and MB groups received appropriate damage to the target structure, and that the MS lesion produced noticeable but asymmetric denervation of acetylcholine activity in the HF.

The first issue addressed by the present research was the effect of MS and MB lesions on the SPE in rats. Figure 2.8 shows that MS, MB and sham surgery all had different effects on the SPE in rats. The left panels in this figure show the mean accuracy at Serial Positions 1, 3, 4, 5 and 7 from the 6 sessions (30 trials) pre-surgery for the 10 MS lesioned rats, 6 MB lesioned rats and 10 sham-control rats. Note that because the MB group were originally some of the members of the sham group, the baseline data for the MB group was obtained from the last 6 sessions, from the total 18 sessions of training, following sham surgery. The right panels in Figure 2.8 show the mean accuracy at Serial Positions 1, 3, 4, 5 and 7 from sessions 7 to 18 after MS, MB and sham surgery. As the first 6 sessions of training post-surgery revealed disruptive effects of surgery even for the control rats (see Figure 2.9 below), these data were considered as a period of re-familiarisation with the task and were excluded from the data presented in Figure 2.8. Accuracy was measured using the percentage of correct returns to a list arm during the test phase of a trial at a given serial position.

Pre-surgery, rats showed a SPE with primacy and recency present. That is, accuracy was higher at the two ends of the list compared to the middle positions. The presence of a SPE was confirmed by the existence of a significant quadratic trend in accuracy across serial positions for rats in the MS, MB and sham groups pre-surgery, [$F(1,9)=6.05$, $p<.05$; $F(1,5)=6.67$, $p<.05$ and $F(1,9)=12.96$, $p<.01$, respectively]. Figure 2.8 also shows that after the 6-day recovery period post-surgery, rats in the sham-control condition continued to show a serial position curve with both primacy and recency effects present. Analyses for the sham-control group revealed no effect of surgery on performance ($F<1.0$) and that a significant quadratic trend in accuracy was still present [$F(1,9)=31.12$, $p<.001$].

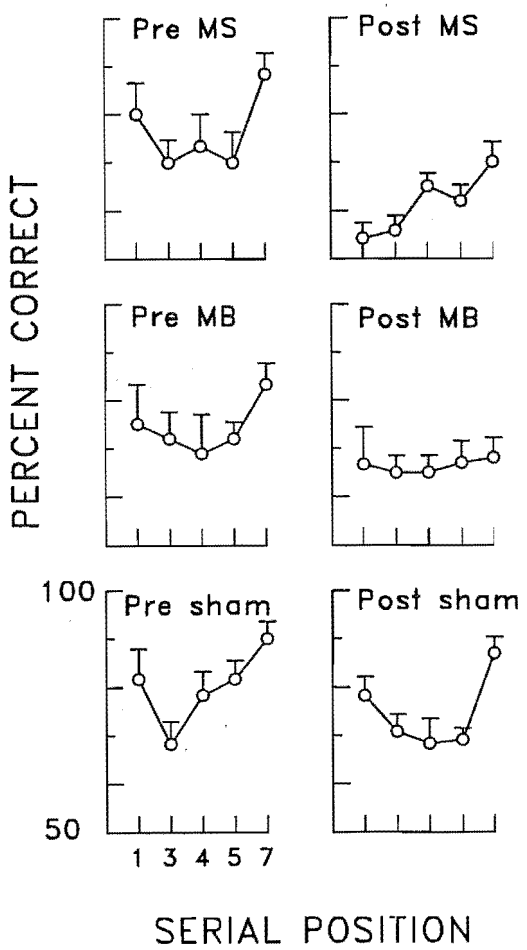

FIG 2.8 Percent correct recognition at Serial Positions 1, 3, 4, 5 and 7 in a 7-arm list prior to (left column of graphs) and following (right column of graphs) surgery. The top, middle and bottom rows of graphs show data from rats in the MS, MB and sham-control conditions, respectively. For each graph, the five points on the X-axis represent Serial Positions 1, 3, 4, 5 and 7. The Y- axis gives percent correct, gained by averaging over all subjects in a group for a given serial position. For the pre surgery graphs the measure of percent correct was obtained from 6 sessions of training immediately prior to surgery. For the post surgery graphs the measure of percent correct was obtained from the 7th to 18th sessions of training following surgery. Error bars indicate the standard error for each data point.

Both MS and MB lesion groups showed impaired SPR performance after surgery. Rats with a MS lesion showed two major changes from their pre-surgery performance: overall accuracy decreased and the primacy effect ceased to be evident. The decrease in accuracy over all serial positions was confirmed by a significant effect of surgery (pre versus post for the MS group) on performance [$F(1,9)=26.22$, $p<.001$]. A significant decrease in accuracy occurred at both Position 1 [$F(1,9)=13.33$, $p<.05$] and Position 7 [$F(1,9)=18.47$, $p<.01$]. However, despite a significant decrease in accuracy for Position

7, Figure 3 and the subsequent analyses demonstrated that a recency effect was maintained. Across serial positions post-surgery, accuracy was poorest for Position 1 and greatest for Position 7. Trend analysis revealed a significant positive linear component [$F(1,9)=7.91$, $p<.05$] in accuracy across serial positions but no evidence of a quadratic trend ($F<1.0$) in the MS group. Therefore, despite accuracy decreasing overall, a recency effect was maintained in that accuracy remained superior for positions late in the list relative to positions early in the list. However, the primacy effect disappeared: accuracy was no longer superior at early list positions relative to middle list positions.

The MB lesion did not result in the same changes in performance observed in the MS rats post-surgery. The MB lesion did not significantly decrease overall performance ($F<1.0$), but it did eliminate evidence of primacy and recency effects. Therefore, despite the existence of a significant quadratic trend across serial positions pre-surgery, MB rats failed to show the same trend post-surgery. Furthermore, following the MB lesion, rats did not show a significant linear change in accuracy across serial positions ($F<1.0$) as the MS group did.

A second issue of interest in the present study was the robustness of MS or MB lesion effects on memory for list arms. The robustness of lesion effects was assessed in two ways: firstly, by observing performance in the basic procedure over several 6-session blocks of training post-surgery and secondly, by examining whether post-surgery performance can be altered by increasing the time in which rats were exposed to list arms. The robustness of the lesion effects with extended training was examined by plotting performance in rats following MS, MB and sham surgery over a succession of 6-session blocks, as shown in Figure 2.9. The top, middle and bottom rows in Figure 2.9 show data following the MS, MB and sham lesion, respectively. The left panel on each row in Figure 2.9 shows accuracy at Serial Positions 1, 3, 4, 5 and 7 in the first 6 sessions post-surgery. The 3 subsequent panels (for the MS group) and 2 subsequent panels (for the MB and sham groups) are successive 6 day blocks post-surgery. Each

data point represents the average percentage score from all the rats in a group over the 6 sessions of training in a block.

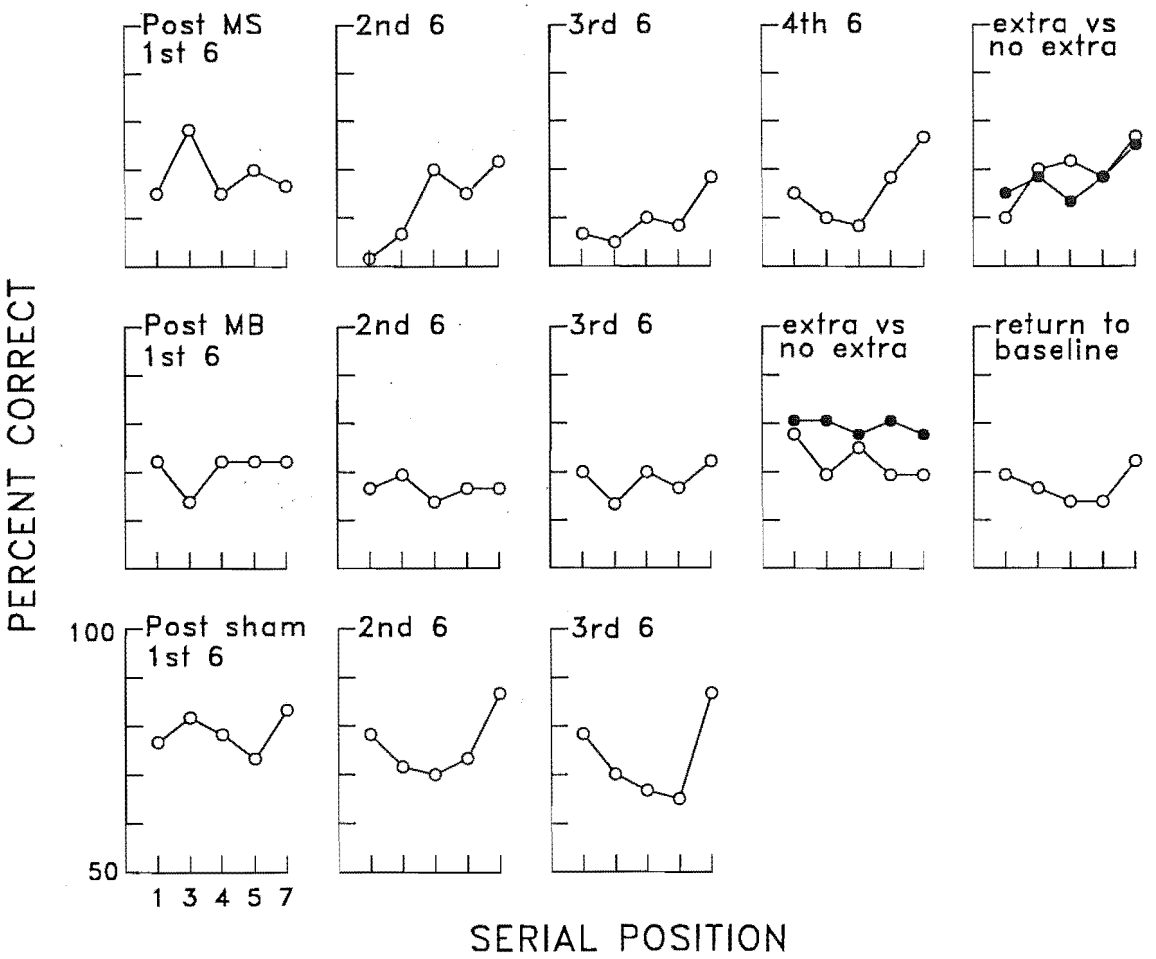

FIG 2.9 Percent correct at Serial Positions 1, 3, 4, 5 and 7 in a 7-arm list for MS, MB and sham-control rats broken down into sequential 6-session blocks of training post surgery. For each graph, the five points on the X-axis represent serial positions 1, 3, 4, 5 and 7 respectively. The Y-axis gives percent correct, gained by averaging over all subjects in a group for a given serial position across all 6 sessions shown in a graph. Also shown for the MS and MB rats is a graph showing accuracy across serial positions during the 6 sessions of extra-arm exposure (closed circles) interpolated with 6 sessions of baseline with no extra exposure (open circles).

The first block of training post-surgery shows that immediately following MS, MB and sham surgery, there was no evidence of a SPE. No significant trends in accuracy across serial positions were evident for any group. However, following the first block post-surgery, the trends summarised in Figure 2.8 were found to be robust across the subsequent 6-session blocks of training for all groups. Following a sham lesion, rats displayed a significant quadratic trend in accuracy across serial positions in Blocks 2 [$F(1,9)=24.59$, $p<.001$] and 3 [$F(1,9)=11.29$, $p<.01$]. Following a MS lesion, rats displayed a significant linear trend in accuracy across serial positions in Block 2 [$F(1,9)=13.95$, $p<.01$], Block 3 [$F(1,9)=5.81$, $p<.05$] and Block 4 [$F(1,9)=4.94$, $p<.05$], and failed to demonstrate a significant quadratic trend in any block. Also, the MS rats displayed a main effect of pre- versus post- surgery on accuracy in Block 2 [$F(1,9)=11.62$, $p<.01$], Block 3 [$F(1,9)=34.09$, $p<.001$] and Block 4 [$F(1,9)=5.48$, $p<.05$], indicating that accuracy was reduced across all serial positions for each block post-surgery. Following a MB lesion, rats failed to show any significant trends in accuracy across serial positions in any block or any significant reduction in accuracy overall.

The second means of examining the robustness of the lesion effects for the MS and MB rats was to provide them with extended exposure to list arms during presentation. To extend the time spent down each arm during the presentation phase, the amount of chocolate placed at the end of each arm was extended from the baseline 1 piece to 3 pieces of chocolate. This manipulation was effective in extending the period of time that rats spent down each arm in the list from an average of 53 s to 82 s per rat in the MS group, and from an average of 51 s to 87 s per rat in the MB group. For both groups, the time spent down an arm because of the presence of extra chocolate was significantly greater than in the baseline condition of no extra chocolate, resulting in a main effect of Condition [$F(1,14)=107.0$, $p<.001$], but no Group by Condition interaction ($F=1.23$).

The effect of increased exposure to list arms on accuracy is shown in Figure 2.9 (see the fifth panel for MS rats and fourth panel for MB rats). These panels show

performance during the 6 sessions of extra exposure to list arms (closed circles) compared to the alternated 6 sessions with no extra exposure to list arms (open circles). For the MS rats, Figure 2.9 and the subsequent analyses showed that despite an increase in exposure time overall accuracy was not improved, nor was the positive linear trend in accuracy across serial positions altered. For the MB rats, Figure 2.9 suggests that at Positions 3, 5 and 7 there was some increase in accuracy with extra list arm exposure compared to the baseline sessions. However, an analysis of the effect of extra exposure vs baseline on accuracy revealed no significant effect of Condition or Condition by Serial Position interaction. It may have been that the 6 sessions of extra exposure influenced accuracy during the interpolated 6 sessions of baseline such that accuracy was improved during baseline, and hence an effect of condition was not able to be confirmed for the MB rats. To check this possibility, a final 6 sessions of training under baseline conditions, (see fifth panel in middle row of Figure 2.9), was conducted for the MB rats, to observe whether accuracy in the baseline declined when training was not interpolated with the extra-exposure condition. However, there was no significant difference revealed in accuracy between this baseline conducted without interpolated training and the 6 sessions of extra-arm exposure. Therefore, despite spending a significantly longer time down each list arm when extra chocolate was available, both groups failed to show any statistically reliable alterations in their post-surgery SPR performance. Thus, the effects of lesions on SPR performance appeared to be invariant with extended post-surgical training.

DISCUSSION

In summary, the results from Experiment 2.3 showed that both MS and MB lesions resulted in an impairment of memory for list items. However, the two lesions had differential effects. Specifically, the MS lesion caused a substantial reduction in overall accuracy, concurrent with a loss of primacy but retention of recency effects. By comparison, the MB lesion was far less disruptive to performance in that overall

accuracy was not significantly reduced, although the primacy and recency effects were removed. The effect of the MS lesion in the present study was similar to that observed by Kesner et al. (1988). However, the present demonstration was free of the ambiguity arising from unclear primacy and recency effects seen in rats prior to surgery in Kesner et al's study. The present study not only clarifies Kesner et al's original observations but also extends them by showing that the effect of a small MS lesion was robust with continued training and with extra exposure to list arms. Further, the present research demonstrated that damage in a structure other than the MS but which is also connected to the HF (i.e. the MB) produced a pattern of impairment different from that observed following MS damage.

A further difference between the present study and that of Kesner at al. (1988), to do with the number of trials per session, has proven to be informative about the nature of the impairment shown by the MS group. In the present study five identical trials were conducted within a session, whereas Kesner et al. only used one. An analysis of changes in performance as a product of trial in the session showed that for the MS group alone, accuracy steadily decreased. This result suggests that the general impairment observed at all serial positions for the MS group may result from proactive interference arising from events in earlier trials. An analysis of accuracy at Serial Positions 1, 4 and 7 when each position was tested in the first, third or fifth trial of the session indicated that for all 3 groups pre-surgery, but for only sham-control and MB groups post-surgery, there were no significant changes in accuracy at a given serial position or overall. This lack of influence of previous trials on later ones was the same as observed in Experiment 2.1. However, there was a significant proactive interference effect from previous trials evident in the MS group post-surgery. Specifically, in the MS group accuracy (across Serial Positions 1, 4 and 7) was on average 69% for the first trial of the day, 62% for the third and 49% for the fifth. This reduction in accuracy across trials was significant [$F(2,18)= 7.08$, $p<.05$], but there was no significant interaction of serial position by trial of the day. Therefore, MS lesion damage may result in a sensitivity to proactive interference effects from previous trials, although this

does not account for the differential influence of MS damage on the primacy and recency effects.

The above results indicated that of the two brain regions investigated in the present study, the MS region appears to play a more critical role in memory and lesions to it produce deficits similar to those observed in humans with disorders such as AD and KS. For example, MS lesions not only resulted in a general pattern of impairment (i.e. loss of primacy but intact recency) which mimicked that found in these disorders, but also an increased sensitivity to proactive interference effects from previous trials. Similar disruptions to memory for list items has been shown in AD and KS following previous list learning, albeit with lists containing different stimulus items, e.g. Krammer et al. (1988) and Delis et al. (1991). Finally, not only do MS rats display these similarities to AD and KS subjects but they also mirror the lack of improvement shown by AD sufferers under procedures that promote an increase in accuracy (e.g. Miller, 1971).

At a neurological level of explanation, it has been suggested that MS damage has an effect on primacy via a disruption of acetylcholine activity in the hippocampal formation (Kesner et al., 1988). This view is supported by the observations from a number of independent lines of research, such as studies which have examined - lesions to the dorsal hippocampal formation in rats (Kesner & Adelstein, 1989; Kesner et al., 1988); humans with hippocampal damage (Milner, 1978); humans with pharmacological blockade of CNS acetylcholine activity (Crow & Grove-White, 1973; Frith et al., 1984) and subjects with AD or KS who display neuropathology in the MS (e.g. Adelstein et al., 1992; Baddeley & Warrington, 1970). The subjects in these various studies all show similar patterns of list memory disruption as rats with MS lesions. However, pharmacological and clinical studies do not allow the specific assessment of brain region function, thus the present study is a more direct assessment of the possible role of the MS in memory than is provided by many of these other lines of research. Additional support for the role of the MS in memory (via its

influence on hippocampal cholinergic activity) could potentially have come from a comparison of impairments in rats with large versus small amounts of hippocampal AChE depletion. However, the relatively few observations available for each rat under the present procedure meant that the degree of impairment shown by any one rat is hard to ascertain. Furthermore, the MS rats in the present study exhibited only a limited range of AChE depletion across the group and because of the loss of several slides in histological processing it was impossible to determine whether greater depletion correlated with greater levels of memory disruption. Potentially, a larger MS lesion (and thus greater reduction in hippocampal acetylcholine) than used here may have provided enough data to allow a comparison of cholinergic disruption with the degree of memory disruption. However, a large MS lesion was not investigated in the present experiment because previous indications were that such a lesion was likely to produce extremely severe disruption in performance and thus render any comparisons uninformative (Kesner et al., 1988). Therefore, while cellular damage in the MS causes a disruption to SPR performance it remains to be firmly established that this is because of a disruption in hippocampal acetylcholine.

Although the MB region receives input from the MS and HF and projects to the HF (Swanson 1982, 1984), it does not appear to serve the same role as the MS or HF in memory for list items. For instance, although the MB group was similar to that of MS group in that for both groups the primacy effect was absent following surgery, the two groups were dissimilar in that only MB damage resulted in a removal of the recency effect as well. This finding suggests that the MS and MB regions are involved in different aspects of memory functioning. Furthermore, the lack of overall reduction in accuracy following the MB lesion suggests that damage in the MB is not as disruptive to list-item memory as damage in the MS or HF. There are, however, similarities between the effects of MB (in the present study) and nucleus basalis magnocellularis lesions (observed in other studies) on memory for list items. For example, Kesner & Adelstein (1989) found that although small and large nucleus basalis lesions did not reduce overall performance, there was no evidence of primacy or recency effects post-surgery

for the large nucleus basalis group. In general, despite a number of studies examining the effect of MB lesions using a variety tasks, the role of the MB region in memory remains equivocal. The lack of overall reduction in memory performance on the SPR task following a MB lesion is consistent with previous research which has shown none or only limited impairment resulting from MB lesions in DNMTS tasks (e.g. Aggleton et al., 1990; Aggleton et al., 1991) and an 8-arm radial maze task (Jarrard et al., 1984). However, other studies have reported a significant impairment in memory following a MB lesion in DMTS and the 8-arm radial maze task (Saravis et al., 1990) and T-maze alternation tasks (Field et al., 1978; Beracochea & Jaffard, 1987). Thus, the extent to which, or conditions under which, the MB may play a critical role in memory performance are currently unclear.

Interpreting the differential effects of the MS and MB lesions on the SPE in terms of disruptions to 'memory processes' is made problematic because of the variety of theoretical interpretations that have been suggested to account for primacy and recency effects. Some theories attribute primacy and recency effects to differential processing within long- or short- term memory (e.g. Atkinson & Shiffrin, 1968; Craik, 1970; Glanzer, 1972). Other authors have accounted for primacy and recency in terms of the action of retroactive and proactive interference (e.g. Waugh, 1960; Postman & Stark, 1968) or in terms of the delay-reduction to reinforcement properties of stimuli that occur in different serial positions (e.g. Wixted, 1989). However, as noted by a number of authors, none of the theories are able to account for all the data available on the SPE (Baddeley, 1986; Koppenaal & Glanzer, 1990). Therefore, interpreting the effects of lesions on list item memory in terms of a single model of memory is likely to be of limited value, and the present study was not intended to decide between them. Rather, the focus of the present research was on the degree to which the MS and MB regions played a differential role in memory and the degree to which their roles (as revealed in the present instance by the SPR task) could be integrated with other lines of research implicating them in memory function.

2.4 Summary of the Serial Probe Recognition Research

The three experiments presented in Chapter 2 constitute a body of research which had several aims. Experiments 2.1 and 2.2 were conducted because of the lack of research which has provided convincing evidence for the existence of a SPE in rats; these two experiments were necessary prior to conducting an investigation of lesion effects. Experiment 2.1 investigated whether a clear and robust SPE could be established using a 7-arm list presented in a 12-arm radial maze as an attempt to overcome the weaknesses apparent in many studies which have examined memory for list items in rats. The results indicated that the procedure used here was sufficient to produce a convincing SPE. Experiment 2.2 examined the SPE in greater detail by assessing the effect of two manipulations designed to reduce recency but leave primacy relatively intact. The changes which occurred in the SPE with delays of up to 30 s and an event interpolated into the delay were similar to those observed with human subjects. This finding supports the conclusion that the primacy and recency effects observed in rats are very similar to those observed in humans and that these two aspects of performance are to some degree independent. These similarities imply that the SPE observed in rats and other species is analogous and thus strengthens the position that relevant data obtained from different species may be integrated.

Experiment 2.3 investigated the effect of MS and MB lesions on the SPE in rats. The effect of lesions on SPR performance was an important aspect of determining the functional roles of the MS and MB in memory performance. Previous research with rats indicates that discrete damage to the MS or MB can result in significant memory impairments in a variety of memory tasks. The general impairment observed in SPR performance for the MS group, and to some degree with the MB group, was consistent with their potential role in memory. Previous research with human subjects that display neurological damage in the MS and/or MB (e.g. AD and KS), or pharmacological disruption to the CNS cholinergic system indicates that primacy is severely reduced or eliminated while recency is mildly reduced or unaltered. Therefore the precise pattern

of impairment to the primacy and recency effects observed following selective lesions to these structures was of interest in the present study.

The rats with a MS lesion showed alterations in the SPE which were consistent with the memory disruptions observed in AD and KS and under pharmacological cholinergic disruption. In particular, the impairment in SPR performance following MS damage was greatest for the primacy component of the SPE. This reduction in the primacy effect is an aspect of the memory alterations observed in AD, KS and when using pharmacological methods to disrupt cholinergic activity. In addition to the loss of the primacy effect, MS rats displayed a general disruption at all serial positions. An analysis of accuracy as a function of trial in the session was consistent with the suggestion that this general reduction in accuracy was perhaps partly (or wholly) the result of early trials proactively interfering with later ones; an influence which was only present in the MS-lesion group post-surgery. The disruptive influence of previous list trials on later ones is also consistent with the intrusion errors observed in AD and KS subjects when required to recall lists of words in the California Verbal Learning Test. In contrast to the MS lesion, the MB lesion had less of an effect on performance although accuracy at both the primacy and recency ends of the SPE was reduced. Like the MS lesion the effects of MB lesions were robust with continued training, thus supporting the conclusion that both brain regions play a role in normal memory function. However, the greater impairment following the MS lesion suggests that at least in the SPR task this brain region is more critical and may underlie the memory deficits observed in AD and KS as well as subjects given scoploamine. A common aspect of the neurological alterations which take place in AD, KS, administration of scopolamine, and MS damage is a reduction in hippocampal acetylcholine activity. Thus, the similarities in the patterns of impairment observed across these groups is consistent with the possibility that cholinergic activity in the HF plays an important role in normal memory function.

Despite some success at providing results which can be integrated into the existing literature implicating the MS in memory function, there were several aspects of the task

which restricted its further utility in the present research. Firstly, it may have been that the arrangement of delays or retroactive interference into the SPR task (of the type examined in Experiment 2.2) would have been comparatively more disruptive to the MS rats than the control rats. Such an investigation would have been valuable in providing a potential integration with a large variety of other relevant research issues (e.g. delayed recall or recognition performance and the influence of interference). However, such an investigation was not conducted with the lesioned animals here because of the severe disruption already shown across all serial positions by the MS-lesioned rats.

A second problem that arose with the present SPR research was to do with the stability of behavior. The results of Chapter 2 indicated that the SPE and lesion effects on it were robust and general patterns of behavior were typically consistent, however a close examination of data across blocks of training shows that performance did tend to shift around. For example, in the second to fourth block of training post-surgery for the MS group (see Fig. 2.9, Experiment 2.3), accuracy at Position 4 shifted from 70% to 60% to 58%, while accuracy at Position 5 shifted from 65% to 58% to 68%. Such tendencies of the data to shift may have been because of the difficulty in controlling the experimental conditions. As with all manual maze-based procedures there was great difficulty in maintaining precise control over factors such as trial length and delays. Subsequent attempts in the laboratory to develop an automated radial-arm maze procedure which allow precise control over multiple presentation of SPR trials have been unsuccessful in establishing clear primacy effects, although recency effects were often obtained.

The labour-intensive nature of the procedure meant that very few trials and conditions were possible, and this is problematic when it is desirable to use bias-free measures such as *Log d* to measure recognition (see Section 1.3.2). Because the SPR procedure requires a choice between concurrent alternatives, the possibility exists for idiosyncratic biases to influence our measures of memory performance. Experiment 2.2 described a procedure for gaining *Log d* for a group of rats in the current SPR task.

However, because few training trials per rat meant that only group data could be analysed, the bias that was separated from the measure of *Log d* in the present study was not individual idiosyncratic bias, but rather any tendency of the group as a whole to favour a particular stimulus arm. Unfortunately, the grouping of individual scores into a single response-matrix is less preferable than obtaining the mean of individual *Log d*s because the individual biases come to be counted as true errors rather than bias and this confounding of bias with error may affect conclusions about accuracy. For example the following set of hypothetical *Log d*s presented in the second column below were calculated with bias set at 0.525 (i.e. a constant preference to respond on one choice alternative over the other). In the last column the *Log d*s were calculated from the same number of correct and error responses, but bias was ignored by using the log ratios of total correct to total error responses (elsewhere this measure has been called *Logit p*). Equation 1 was fitted to *Log d* s in both columns using the delays in the first column.

Delay (s)	Log d (bias=.525)	Log d (bias=0)
1	1.357	1.120
4	1.001	0.793
8	0.674	0.507
16	0.303	0.218
32	0.061	0.043

By accounting for the influence of idiosyncratic bias, Equation 1 results in a *b* (rate of forgetting) of 0.100 and *Log do* (performance at a 0 s delay) of 1.5. However by assigning biased responses to error cells, and hence ignoring the influence of idiosyncratic bias, the *Log d* values are altered and the result is a slight increase in the rate of forgetting (*b* now equals 0.111) and a reduction in delay-independent performance (*Log do* now equals 1.246). Therefore, individual performance scores are desirable, but unfortunately practical considerations mean that these are not typically obtainable in SPR maze research.

Notwithstanding the problems noted above with the use of the maze-based SPR procedure, the research reported in Chapter 2 made two major contributions relevant to an understanding of the neurological bases of learning and memory. Firstly, the development of our knowledge regarding memory processes in the rat by demonstrating a clear SPE with both primacy and recency effects present, and in many ways analogous to that observed in humans. Second, the further development of our knowledge of the role played by two brain structures implicated in memory and connected to the HF. However, although the SPR procedure was necessary for examining the effect of MS and MB lesions on the SPE, the interaction between lesion effects and manipulations in variables such as delay, retroactive and proactive interference may be better examined using the operant DMTS procedure. This procedure allows precise control over variables such as delays and the scheduling of events during a trial. Because many animals can be run at once, and it is possible to conduct a large number of trials in any given session, the use of measures such as *Log d* and quantitative memory models is more easily accomplished with individual subjects. Furthermore, there has already been some use made of the DMTS procedure when investigating the effects of interference on memory (e.g. Jans & Catania, 1980; White, 1985; Edhouse & White, 1988) and lesion effects on memory in monkeys and rats (e.g. Aggleton & Mishkin, 1983, 1985; Dunnett, 1985; Dunnett et al., 1989), as well as use with human subjects with neurodegenerative disorders (e.g. Sahakian et al., 1988; Kopelman, 1991; Money et al., 1992). Therefore, an automated DMTS task was used in Chapter 3 to further explore MS and MB lesion effects in rats and thereby investigate several issues of importance in the attempt to integrate the various lines of evidence indicating a role of these brain regions in memory.

Chapter 3 THE EFFECT OF MEDIAL SEPTUM AND MAMMILLARY BODY LESIONS ON DMTS PERFORMANCE

The three experiments described in Chapter 3 investigated the effect of MS and MB lesions on memory performance in rats using an automated DMTS procedure. Experiment 3.1 examined the effects of MS and MB lesions on performance in the basic task as well as an investigation of performance in these groups when levels of retroactive or proactive interference were increased. Experiments 3.2 and 3.3 were a further and more systematic investigation of the interaction between lesion effects and proactive / retroactive interference influences on memory performance in the DMTS task.

EXPERIMENT 3.1 Lesion Effects on DMTS Performance

As discussed in Chapter 1, both the MS and MB brain regions have been implicated in memory function. The MS region has been implicated in the memory impairments observed in both AD and KS particularly via its cholinergic projection to the HF (Arendt et al., 1983; Antuono et al., 1980). Consistent with a potential role of the MS in memory (via the supply of acetylcholine to the HF) are the findings of studies which show that pharmacological disruption of acetylcholine in humans and nonhumans often results in similar memory impairments as observed in AD and KS (Spencer et al., 1985; Dunnett, 1985; Kirk et al., 1989; Crow & Grove-white, 1973; Frith et al., 1984; Caine, 1981; Kopelman & Corn, 1988). In addition, there is a considerable amount of evidence from studies which have employed a variety of tasks that lesions to the MS area in rat brains results in significant memory impairments (see Section 1.2.3 for a review). With respect to the MB, this regions potential role in memory has been indicated by the findings of several studies which indicate that KS subjects who displayed memory problems typical of their disorder, reliably possessed damage in the

MB (Mair et al., 1979; Mann & Pickering, 1988). Furthermore, there is also some evidence from the animal lesion literature that damage to MB region results in memory impairments (see Section 1.2.4 for a review). Thus, the evidence reviewed in Chapter 1 supported the possibility that both the MS and MB regions serve a role in memory function.

Although many of the nonhuman lesion studies show a disruption to performance following MS and MB damage, the effects of such damage on tasks analogous to those used in the human research has not been adequately examined and a systematic comparison of MS and MB lesion effects has not been conducted. Yet such a comparison is desirable if we are to determine the extent to which these two structures, both implicated in memory and both connected to the HF, perform dissociable roles in memory function. Furthermore, a number of previous investigations have used tasks which are ambiguous in terms of the degree to which memory, as opposed to other processes, was involved in the behavioral impairment (e.g. task acquisition, motor-performance changes). In order to integrate more successfully the existing research it is therefore desirable to examine the effects of MS and MB damage in rats using a task analogous to that which has provided informative results in the human research - such a task is DMTS.

Procedures such as DMTS have been used extensively in human memory research to separate delay-dependent aspects of performance (i.e. rate of forgetting) from delay-independent aspects (e.g. 'recall' or 'retrieval'). Studies investigating delayed recognition or recall tasks such as DMTS and the Brown-Peterson show an impairment in performance with AD, KS subjects as well as people administered anti-cholinergic drugs. However, these human studies have not conclusively settled the question of whether the memory impairments observed are best characterised as delay-dependent or delay-independent in nature. For example, despite several authors concluding that the memory impairments exhibited in DMTS performance by AD and KS subjects is reflected in a greater rate of forgetting (e.g. Sahakian et al., 1988;

Oscar-Berman & Bonner, 1989), a number of other studies show that the impairment may be better characterised as an alteration in delay-independent processes such as encoding or retrieval (e.g. Flicker et al., 1984; Kopelman, 1985, 1991; Kinsboune & Wood, 1975; Mair et al., 1979). Thus, the relevant human data do not indicate whether a delay-dependent or a delay-independent alteration in performance might be consistent with MS or MB damage.

As with the human research, what relevant nonhuman research as exists does not clearly indicate what the potential effects of MS or MB damage might be on DMTS performance. In particular, two lines of evidence provide circumstantial evidence that the cholinergic supply of the MS to the HF is important for normal performance in DMTS tasks. Firstly, several studies have shown that accuracy decreases in a delay-independent fashion as the degree of cholinergic disruption increases (e.g. Kirk et al., 1988; Dunnett, 1985 - see Fig. 1.6, Section 1.2.1). By contrast, disconnection of the MS (amongst other brain regions including the MB) from the HF via a fimbria-fornix lesion appears to result in an increased rate of forgetting (Aggleton et al., 1991; reanalysis of Dunnett, 1985 - see Fig 1.10, Section 1.3.2). Therefore, as was the case with the human experimental data, the relevant nonhuman studies imply that MS damage may result in an impairment to DMTS performance. However, it is not clear whether such a disruption may be in terms of an actual increase in the rate of forgetting (i.e. delay-dependent) or in terms of other aspects of performance (i.e. delay-independent).

With respect to DMTS performance following MB damage there is some existing evidence that performance is not impaired post-surgery. For example, Aggleton et al. (1991) found that rats with MB lesions were unimpaired in an automated DMTS task relative to controls. Such a finding with MB-lesioned rats in the automated DMTS procedure is consistent with the lack of effect observed in a Y-maze DNMTS procedure (Aggleton et al., 1990) and the minimal impairment (compared to MS-lesioned rats) in the SPR procedure in Experiment 2.3. However, the lack of severe memory

impairments following MB damage needs to be further established because a number of other studies have found impairments post-surgery (e.g. a delay-dependent deficit in T-maze alternation, Tako et al., 1988; and a delay-independent change to performance in delayed nonmatching in an 8-arm maze, Saravis et al., 1990). Thus, with respect to the MB region, its role in memory is equivocal and more research needs to be conducted to establish the conditions under which an impairment may be observed, if at all, following damage. In conclusion, it appears that the comparison of MS and MB lesion effects on DMTS performance is worth a thorough investigation in order to determine which aspects of performance are affected following damage to these structures (i.e. in terms of delay-dependent or delay-independent alterations).

The effect of MS and MB lesions on memory was assessed in the present experiment by using a similar DMTS task as used previously by a number of researchers (e.g. Dunnett, 1985; Aggleton et al., 1991). The DMTS task allows a distinction between delay-dependent and delay-independent aspects of performance; this distinction is important if we wish to examine changes in memory performance and draw comparisons to the human research. The DMTS task allows a measurement of performance at a delay of 0 s and thus provides a measure of accuracy which is free from any degradation resulting from an actual decay in memory for the item, and therefore provides a measure of delay-independent performance. Performance over the whole range of delays (as assessed by the slope of the forgetting function) provides a measure of the rate of forgetting or delay-dependent aspects of performance which is independent of the ability to recognise a stimulus without a delay (0 s performance). Analytically these two aspects of performance can be separated with the use of a quantitative models such as Equation 1 or 2 fitted to bias-free measure of accuracy - *Log d* (Section 1.3.2 reviewed the benefits of this approach). Equation 1 (White & McKenzie, 1982) provides a measure of 0 s performance (*Log do*) and rate of forgetting (*b*) by fitting a negative-exponential equation to the bias-free measure of accuracy - *Log d,* as a function of delay. Equation 2 (McCarthy, 1981) also provides two similar parameters - *Log do* and *h* respectively, by fitting a rectangular-hyperbolic function to

Log d. Thus, the procedural and analytical techniques exist for the comprehensive analysis of MS and MB lesion effects on different aspects of memory task performance.

Experiment 3.1 was divided into four parts. Part 1 assessed the ability of Equations 1 and 2 to describe the performance of rats in the present DMTS task in order to arrive at the one most suited for the present analysis. Although a great deal of support exists for the ability of both Equations 1 and 2 to describe human and nonhuman performance in DMTS tasks (McCarthy & White, 1987) and to provide parameters of behavior that are empirically independent (White, 1985; Edhouse & White, 1988), the equations themselves have not yet been applied to animals that have undergone lesion surgery. Because there was no *a priori* reason to choose one model over the other an empirical comparison was made in Part 1 in order to determine which was the most suitable for the current purposes. The models were compared on the basis of ability to fit the data (variance accounted for and mean squared error), the ability to return unique parameters with a low confidence interval, and whether the models returned parameters that were independent of one another.

Parts 2-4 examined lesion effects and the interaction between lesion effects and interference on recognition accuracy in the DMTS task. Following baseline training, rats were either given a radiofrequency MS, MB or control-sham lesion in order to observe the effects of surgery on DMTS performance. By comparing the measures of forgetting rate and delay-independent performance obtained pre- and post-lesion it was possible to evaluate each lesions effect on these separate aspects of behavior (Part 2). As was discussed above, it is difficult to predict the effect of MS and MB lesions on the performance measures obtained from a quantitative model. Although the human neuropsychological research, pharmacological research and previous rat lesion research indicate that memory will be disrupted following MS or MB damage, the nature of this disruption in terms of delay-independent and delay-dependent changes is uncertain. It may be that either, both or neither of the parameters which describe rate of forgetting and 0 s delay performance are altered by a MS or MB lesion. Although,

given that there is more systematic support for the role of the MS in memory than the MB, it is expected that damage in the MS is (as was observed in Chapter 2) more likely to result in significant memory impairments.

Not only did Experiment 3.1 assess the effect of MS and MB lesions on the standard DMTS task, but also under conditions of arranged 'interference' (Part 3). Human research has demonstrated that a feature of AD and KS is the high degree of susceptibility to the interfering effects of events which occur during and prior to the current trial (i.e. retroactive and proactive sources of interference). For example, in delayed recall tasks such as the Brown-Peterson, AD subjects show a very severe impairment in performance when required to tap their finger or do arithmetic during the delay compared to when such requirements are not present (Morris, 1986; Sullivan, Corkin & Growdon, 1986). A susceptibility to proactive interference is indicated by the tendency to perseverate on previously recalled words, pictures or lists in AD and KS subjects (e.g. Butters, 1985; Butters et al., 1987; Delis et al., 1991; Kramer et al., 1988).

If damage to the MS or MB regions contributes to the susceptibility to interference in human disorders such as AD or KS, then it may be that rats with damage in these areas will display a greater susceptibility to the disruptive effects of manipulations which interfere with memory performance in intact animals. Animal research has shown a number of delay 'events' to be effective in disrupting performance and two of these retroactive interferers were used here. First, the effect of turning on a houselight during the delay interval between initial stimulus presentation and subsequent recognition has been shown to be effective in reducing accuracy in pigeons run in procedures which use key colours as stimuli (Roberts & Grant, 1978; Jans & Catania, 1980; White, 1985). Specifically, White (1985) demonstrated that the presence of the houselight in the delay resulted in an increase for *b* parameter obtained from Equation 1. That is, turning on the houselight increased the rate of forgetting but left delay-independent performance unchanged. Although the present DMTS task used lever-position as stimuli, rather than

key colour, the presentation of levers was simultaneously paired with light presentation above them. Therefore, a houselight may be an effective disruptor in this procedure depending upon the degree of stimulus control exerted by the light component of the stimulus.

A second potential source of retroactive interference examined in Part 3 was the 'free' delivery of a food in the delay. Free food access was shown in Experiment 2.2 to be particularly disruptive to SPR performance in intact rats. As with the houselight-in-the-delay manipulation, although the effect of free food access has not been examined with rats in the automated DMTS task, there are indications from previous pigeon research that this manipulation will be particularly disruptive. For example, Jans & Catania (1980) demonstrated that free access to food in the delay can cause a great deal of disruption to performance in a DMTS task with pigeons. In a reanalysis of their data, White (1985) demonstrated that as with houselight presentation, the effect of free food in the delay was to increase the rate of forgetting, but leave delay-independent measures of performance unchanged. To date, the effects of retroactively interfering events have not been investigated with MS or MB lesioned rats using the DMTS task. However, if rats with MS or MB lesions are more susceptible to the potentially interfering effects of retroactive interference, then an increase in the rate of forgetting (beyond that shown by control animals) is expected when free food or a houselight are made present during the delay.

Apart from examining the interaction between lesion effects and retroactive interference, Part 3 also examined the interaction between lesions and proactive interference. In the basic DMTS task, the most obvious source of proactive interference is from behavior and stimuli present on previous trials. That is, when the trial immediately previous to the current one involved a different correct stimulus or response, then the subject may be more likely to make an error than when the previous stimulus or response was the same. The degree of this disruption from previous trials depends on the time interval between trials. That is, the greater the inter-trial interval,

the less such interference occurs. For example, Edhouse & White (1988) and Dunnett & Martell (1990) have demonstrated that reductions in the inter-trial interval degrades performance in the DMTS task in pigeons and rats. In the present experiment the level of proactive interference was increased by reducing the inter-trial interval from a baseline 15 s to 5 s in order to investigate susceptibility to proactive interference. It may be that the increase in proactive interference that occurs when the inter-trial interval is reduced to 5 s is more disruptive in either or both of the lesion groups relative to controls. Supportive of the expectation that MS-lesioned rats may be more susceptible to proactive interference are the findings of the SPR research in Experiment 2.3. Experiment 2.3 found that for the MS-lesion group alone, accuracy at all serial positions was reduced at later trials in the day relative to earlier ones. That is, events in early trials appeared to proactively interfere with performance on trials later in the session.

Part 4 examined the effect of a MS lesion that was larger than used in Parts 2 and 3 of Experiment 3.1and in Experiment 2.3. As will be shown, the results of Parts 2 and 3 indicated that unlike the SPR research a relatively small MS lesion was ineffective in producing an impairment in DMTS performance. Therefore, another group of rats received a slightly larger MS lesion in order to produce a greater depletion of hippocampal acetylcholine and thus increase the likelihood of impairing DMTS performance. However, the effect of a larger MB lesion was not investigated. The current MB lesion was effective in removing the majority of the anterior portions of the MB region, and a larger area of damage to this structure runs the danger of destroying other neighbouring brain regions that may produce spurious memory deficits (e.g. the substantia nigra). Therefore, 7 further rats were trained on the basic DMTS task and subsequently given a larger lesion of the MS than had been previously used in Experiment 2.3 and the earlier parts of Experiment 3.1.

METHOD

Subjects

28 naive male Wistar rats, approximately 3 months old at the start of training were used as subjects in Parts 1, 2 and 3. The rats were housed three to four per cage and were maintained at 80-85% of their *ad libitum* body weight with free access to water throughout the study.

Apparatus

Seven similar experimental chambers with wire mesh floors, measuring approximately 24 cm long, 32 cm wide and 20 cm high, each contained an interface panel. In all chambers, reinforcers of 0.1 ml liquid reinforcement (1 part sweetened condensed milk with 14 parts water) were collected at floor level at the centre of the interface panel. In 3 of the chambers a hole was located in the centre of the panel which allowed the cup of a liquid dipper to be presented to rats when reinforcers were delivered. In the other 4 chambers a food well was located in the centre of the panel into which reinforcers could be dispensed via a liquid dropper. In all chambers presentation of reinforcers was accompanied by illumination of a 80 mA light near the food well.

Three manipulanda were available to rats. Retractable levers were located 8 cm above the floor on the left and right side of the interface panel. The levers took between 1 and 2 s to fully insert or retract, but were operable .5 s after starting insertion, or up to .5 s prior to total retraction. In the middle of the opposite wall there was a non-retractable response lever. A single 80 mA white light was located immediately above each lever. There was also a houselight (3 x 80 mA bulbs) located in the centre of the roof of each chamber. Each chamber was itself enclosed within a larger sound-attenuating chamber and a ventilation fan at the rear of each chamber also helped to mask extraneous sounds. The chambers were all in a darkened room

remote from the experimental control system. All experimental events were scheduled and recorded by an IBM-compatible computer running MED-PC software.

Procedure

The present research used *Log d* values obtained from 5 delays in which left and right levers were utilised as stimuli in an automated DMTS procedure. It was originally planned to make use of visual stimuli presented in an operant chamber. To date researchers conducting operant-based DMTS procedures have used left versus right lever position as the stimulus. An advantage of using visual stimuli is that the likelihood of positional biases occurring is reduced because position is unpredictive of 'correctness'. Furthermore the use of spatial stimuli, such as lever position, means that the rat must be required to perform a centering task during the delay to avoid overt (and extremely successfull) rehearsal strategies such as standing on one side of the chamber. However, there was great difficulty training rats in the visual task. Twenty rats were first shaped to lever press in 4 operant chambers, and over the course of 90 - 100 40 min sessions (run 6 days per week) the rats were trained to discriminate between a fast and slow flashing light in a matching to sample procedure. Despite extended training on the basic task and various alterations in the task to shape behavior, as well as correction procedures, no rat ever displayed evidence of being able to discriminate between the lights. Subsequently, another attempt was made to train approximately 24 new rats, in 8 operant chambers using the same basic task except they now had to discriminate between a flashing and constant light. After 80 - 100 sessions only 4 rats showed above 70 percent performance in matching to sample accuracy. These rats had delays gradually introduced, but at very short delays their performance was severely disrupted. Therefore, as noted by other researchers, rats appear to have great difficulty learning conditional discriminations with visual stimuli (e.g. Wallace et al., 1980; Dunnett, 1985). Consequently, despite the potential advantages of non-spatial DMTS procedures, they do not appear to be very easily trainable in rats, and therefore lever position is currently the most sensible choice of stimulus.

Preliminary Training

Prior to training in the actual experimental procedure, all rats were shaped to respond for food reinforcers in the operant chambers. First, rats were reduced to their target weights and for the two days prior to being placed in the chambers for the first time a small amount of the reinforcer was placed in each of the home cages. Rats were assigned to a specific experimental chamber in which they were always run. They were trained in daily 40 min sessions, 7 rats at time (1 rat per chamber), using an autoshaping procedure. Autoshaping involved discrete trials in which either the left or right lever was inserted into the chamber for a period of 12 s. During the time in which the lever was available to the rat, the light above it was turned on and a response on the lever resulted in presentation of .1 ml of reinforcer. If after 12 s, the rat had not responded on the lever, a reinforcer was delivered and the lever was retracted and the light switched off. Fifteen seconds later a new trial began, with insertion of either the left or right lever into the chamber (randomly determined). After 2 sessions of training, the delivery of the reinforcer at the end of the 12 s was discontinued, and the only way in which a rat could gain food was by responding during the time in which a lever was available. After approximately 3 to 8 sessions all rats were responding on both the left and right levers.

Following shaping the lever press response, the response chain of the basic matching to sample task was gradually trained. First, for 2 sessions rats were required to respond on an FR 3 schedule on a lever when it was made available in order to gain access to food. In the subsequent 2 sessions, a trial began with the light above the rear lever being switched on. The rat had to respond on this rear lever once in order to have one of the front levers (accompanied with the appropriate light) inserted into the chamber, and thereby gain food. The next phase of training was the introduction of the actual matching to sample task, which involved the following sequence of events in any given trial:

1. Either the left or right lever was inserted into the chamber (accompanied by the appropriate light being switched on). 0.5 s after the start of insertion, the lever became

responsive to presses from the rat. Whether the left or right lever was inserted into the chamber was determined by a pseudo-random sequence which ensured that no more than 3 sequential presentations of a particular lever were possible (Fellows, 1967).

2. Following 3 presses on the lever, it retracted and the light above it went off.

3. Once the lever was fully retracted, the light above the rear lever came on. A single response to this lever turned the light off and resulted in both the left and right levers being inserted into the chamber (with the appropriate lights being turned on). The rat was required to respond on the central back lever as a centering task, in order to avoid rats adopting a strategy of staying still following initial stimulus presentation. Such a centering task is required in any task which uses position as a stimulus.

4. 0.5 s after they began to insert into the chamber, both levers became responsive to lever presses by the rat. As soon as a response was made on either of the levers, the lights went off and the levers began to retract. If a correct response was made, i.e. to the lever originally responded to during the initial stimulus presentation, the rat gained access to the reinforcer. If an incorrect response was made, i.e. to the lever not initially responded to during initial stimulus presentation, the rat received no reinforcement.

5. Once 4 s had elapsed from the rat making its choice response, both levers had become fully retracted, and an inter-trial interval (ITI) of 15 s was initiated. At the end of this period, a new trial began.

Sessions were run daily for 60 trials, or until 40 mins had elapsed. Once a rat had achieved a minimum of 75% accuracy over 5 sessions in the no-delay task, the DMTS procedure was introduced. The DMTS task involved the same sequence of events as the matching to sample procedure in which the rats had been trained, except that delays were introduced between presentation of the initial stimulus and the subsequent opportunity to recognise it. That is, the delay between retraction of the initial stimulus lever and the opportunity to respond on it again was 6.5, 10.5, 18.5, 26.5, or 34.5 s. Any idiosyncratic latencies to respond on the levers once they were available was not counted as contributing to the delay. In any given session there were 20 trials

scheduled at the 6.5 s delay and 10 trials at each of the other delays. The greater number of trials at the shortest delay was in order to avoid the possibility of not gaining enough errors to enable an accurate measure of *Log d* at this delay. The delay for a given trial was arranged in a pseudo-random fashion in that although the delay for any given trial was unpredictable, delays were arranged equally across trial types and a delay was not repeated until all the other delays had been used. However, the actual number of trials at any given delay in a session varied slightly when sessions stopped after 40 min.

During each delay, rats continued to respond on the back lever. The first response after the delay had timed out resulted in presentation of the two choice levers. Failure to respond on the back lever prevented the delay from ending, and thus did not allow access to the two front levers. Therefore, rats effectively responded on a VI schedule during the delay with inter-response times typically less than 1 s. This basic procedure served as the baseline condition throughout the experiment. Rats continued to be trained daily on the DMTS procedure for 60-80 sessions. After this amount of training, all of the rats reported in the current research were performing consistently above chance at all delays and had reached asymptotic performance as exhibited by: 1. restricted fluctuations (i.e. approximately +/- 10 percent of each rats mean) in overall percent correct session to session for the last 20 sessions; and 2. trends in accuracy across delays that were accurately described by the quantitative models expressed in Equations 1 and 2.

The research conducted in Experiment 3.1 was divided into several sections, which each addressed a separate issue. Part 1 assessed the ability of the two quantitative models to describe rat performance in DMTS. Part 2 assessed the effect of MS and MB lesions on basic DMTS performance. Part 3 varied the DMTS task over several conditions to assess susceptibility to retroactive and proactive interference in lesioned and non-lesioned rats. Finally, in Part 4 the effect of an increase in the size of the MS

lesion was investigated in a new group of rats and compared with the results obtained in Part 2.

Part 1 of the present study compared the adequacy of Equations1and 2 to account for the trends displayed in accuracy across delays displayed by the first 21 rats trained in the present DMTS task. (The remaining 7 rats were only used in Part 4 for the present experiment). Using the last 20 sessions of baseline training (except subject E1R, where the last 25 sessions were used to avoid undefined *Log d* values) *Log d* values at each delay were calculated for individual rats. Both equations were then fitted to the obtained *Log d* values.

Part 2 investigated the effect of lesions on performance in the basic DMTS task. Rats were divided into 3 groups. One group of 8 rats received a small MS lesion, another group of 7 rats received a MB lesion and the other group of 6 rats received a sham-control lesion. Radiofrequency MS and MB lesions were made using a Radionics RFG-4A lesion generator with a 0.25 mm electrode lowered to the appropriate co-ordinates in the brain. Rats were anaesthetized with an i.p. injection of a xylazine (50 mg/kg) / ketamine (100 mg/kg) mixture. The rat was then placed in a stereotaxic apparatus with the incisor bar set at 3 mm below the interaural line. The small MS lesion was made at the midline, 0.8 mm anterior to bregma and 5.0 & 5.8 mm below the dura. For the dorsal site, the temperature was raised to 60º C for 1 minute. For the ventral site, the temperature was raised to 65º C for 1 minute. The MB lesion co-ordinates were 4.48 mm anterior to the interaural line, +/- 0.5 mm lateral to the midline and 8.8 mm below the dura. At each site the electrode temperature was raised to 65º C for 1 minute. For the sham-operated control group, the electrode was lowered into the cortex above the MS but no current was passed. (To maximise the use of subjects, the rats in Experiment 3.1 were also used in Experiments 3.2 and 3.3. Therefore histology was not conducted at the end of the current experiment, but rather upon completion of all the experiments in Section 3.0 - see Appendix A). After 3 days of post-surgery recovery, all rats were placed back in the DMTS procedure and were

trained for a further 25 sessions in Part 2, of which only the last 20 sessions were used to assess performance.

After examining the basic effect of lesions on DMTS performance in Part 2, Part 3 investigated the effect of three different potentially interfering manipulations on performance in the same rats. Each condition was run for 23-25 sessions. In the first condition of Part 3, the ITI was reduced from 15 s to 5 s. In the second condition, the ITI was returned to 15 s, but during the delay between stimulus presentation and subsequent recognition the houselight was turned on. During this condition the houselight was turned on for approximately half of the delay, starting after the first quarter of the delay had elapsed. For example, during the 26.5 s delay, the first 6.75 s the rat was in darkness, during the next 13 seconds the houselight was on, and during the final 6.75 s the rat was again in darkness. The final condition in Part 3 presented free food during the delay. 0.1 ml of the same liquid food used to reinforce correct responses was delivered immediately after a rat had completed the FR 3 on the initial stimulus lever, i.e. at the very beginning of the delay to ensure that the reinforcer was consumed prior to the scheduled end of the delay.

Part 4 of Experiment 3.1 examined the effect of a larger MS lesion on performance in a new group of 7 rats using the basic DMTS task. Rats were pretrained prior to surgery the same as described for the 21 rats used in Parts 1, 2 and 3. The larger radiofrequency MS lesions were made using the same procedure as the MS lesions in Part 2 except that the temperature for the dorsal site was 72^{o} and at the ventral site was 76^{o}. Three days after surgery, the rats were placed back in the basic DMTS task for 25 sessions and performance was assessed for the last 20 sessions of this period.

RESULTS and DISCUSSION

The results of Parts 1 - 4 are presented separately below.

Part 1

Part 1 assessed the adequacy of the exponential and hyperbolic decay models to describe the data obtained from rats in the current DMTS task. Using non-linear least squares regression, Equations 1 and 2 were fitted to the data generated by the 21 rats trained in Part 1. The results, presented in Table 3.1 below, indicated that although both models fitted the obtained data very well the negative exponential (Equation 1) was the more appropriate of the two. Table 3.1 gives the parameter estimates obtained for *Log do* and *b* (Equation 1), as well as *Log do* and *h* (Equation 2) for each subject. Also shown are the standard errors (SE) associated with each parameter obtained, variance accounted for (VAC), mean squared error (MSE) and the degree of dependency (DEP) of one parameter on the other.

Table 3.1 shows that both the exponential and hyperbolic functions provided good descriptions of DMTS performance for individual rats in the present task. With a VAC of 80% or more the exponential function fitted the data from all but 3 rats and the hyperbolic function fitted the data from all but 2 rats. However, the hyperbolic function did not fit the data for one rat at all (D2W), and hence parameter estimates were uninterpretable. A comparison of the VAC and MSE (both of which measure 'goodness of fit') shows that 9 performances were better described by the exponential and 10 were better described by the hyperbolic function, with the VAC for 2 rats the same and the MSE for another 2 rats the same with both models. Therefore, on the basis of goodness of fit the two functions were identical using the data from the present subjects.

TABLE 3.1 Parameter estimates from Equation 1 (Exponential) and Equation 2 (Hyperbolic) fitted to the *Log d* values gained at each of 5 delays from 21 rats performing a DMTS task over the last 20 sessions of training in Part 1. In both models *Log do*, is 0 s delay performance, gained by extrapolation of the function back to the Y-axis. *b* in the Exponential function is a constant rate of forgetting measured across delays; *h* in the hyperbolic function is the half-life of accuracy; i.e the delay required for performance to fall to one half of its initial (*Log do*) level. Standard errors (SE) are given in parentheses for each parameter estimate; variance accounted for (VAC) and mean squared error (MSE) are both measures of the goodness of function fit to the data; dependence (DEP) indicates the degree of independence between the two obtained parameters in a given function.

	EXPONENTIAL					HYPERBOLIC				
SUBJ.	*Log do*	*b*	*VAC*	*MSE*	*DEP*	*Log do*	*h*	*VAC*	*MSE*	*DEP*
B1R	1.16 (.005)	.0508 (.0826)	.979	.001	.72	1.77 (.707)	5.95 (3.79)	.925	.004	.97
B1B	1.62 (.105)	.0305 (.0040)	.958	.003	.73	1.93 (.176)	15.66 (3.19)	.922	.002	.91
BIG	1.76 (.253)	.0237 (.0083)	.741	.023	.72	2.06 (.393)	21.07 (10.02)	.807	.017	.89
B2R	1.40 (.082)	.0357 (.0038)	.973	.002	.72	1.78 (.141)	11.66 (1.83)	.988	.001	.93
B2B	0.93 (.092)	.0363 (.0065)	.927	.002	.73	1.18 (.212)	11.44 (4.05)	.941	.002	.93
B2G	1.18 (.214)	.0477 (.0134)	.865	.009	.74	1.58 (.870)	7.79 (7.25)	.807	.013	.96
B2W	1.00 (.096)	.0557 (.0075)	.966	.001	.73	1.86 (.774)	4.1 (2.45)	.955	.002	.98
C1R	1.38 (.210)	.0303 (.0094)	.791	.014	.72	1.79 (.392)	13.15 (6.04)	.850	.010	.92
C1G	1.57 (.007)	.0293 (.0074)	.855	.011	.72	1.92 (.334)	15.44 (5.96)	.901	.008	.91
C2R	1.52 (.384)	.0716 (.0023)	.846	.014	.77	11.95 (26.45)	0.59 (1.84)	.961	.004	1.0
C2B	1.37 (.125)	.0445 (.0048)	.956	.003	.73	2.13 (.419)	6.56 (2.11)	.973	.002	.96
C2G	1.71 (.160)	.0363 (.0061)	.942	.007	.72	2.03 (.509)	13.17 (6.90)	.881	.014	.92
C2W	1.30 (.207)	.0382 (.0100)	.841	.011	.74	1.72 (.535)	10.11 (5.94)	.866	.009	.99
D1R	1.97 (.172)	.0163 (.0047)	.804	.013	.74	2.10 (.208)	39.83 (13.45)	.850	.010	.84
D1B	0.60 (.150)	.0304 (.0153)	.643	.007	.72	0.65 (.281)	19.71 (21.04)	.576	.008	.89
D1G	0.86 (.058)	.0424 (.0047)	.975	.001	.73	1.12 (.297)	9.29 (4.51)	.924	.002	.95
D2R	1.52 (.100)	.0388 (.0049)	.971	.002	.72	1.96 (.332)	10.39 (3.36)	.957	.004	.94
D2B	1.87 (.128)	.0450 (.0049)	.975	.003	.73	2.70 (.520)	7.32 (2.39)	.970	.004	.96
D2G	2.38 (.208)	.0497 (.0065)	.965	.008	.73	3.89 (.965)	5.47 (2.12)	.971	.007	.97
D2W	1.84 (.299)	.1283 (.0191)	.979	.002	.88	95.31 (478.3)	0.05 (3.02)	undefined parameters		
E1R	2.026 (.144)	.0256 (.0042)	.935	.007	.72	2.276 (.241)	21.51 (5.78)	.939	.007	.88

Another indication of a function's utility is the standard error (SE) associated with the obtained parameter estimates. It is desirable to have smaller SEs relative to the parameter estimate because large SEs are indicative that the estimates themselves can change greatly and still provide the same level of fit to the data. If this were the case then it may become difficult to interpret changes in parameter estimates. Table 3.1 indicates that for both the parameter estimates gained from the hyperbolic model, there is a greater level of error associated with them (relative to the level of the parameter itself) compared to the same estimates from the exponential model. Therefore, the exponential model is superior to the hyperbolic model in producing more precise estimates of delay-independent performance and the rate of forgetting. Hence, with the exponential model it is possible to be more confident in the interpretation of changes in parameter estimates when they occur.

The final measure taken here to compare the exponential and hyperbolic functions was the degree of dependency exhibited by the two parameter estimates within each function. Ideally, because the two parameters obtained from each function describe separable aspects of behavior, the parameters themselves should be independent of one another, i.e. free to vary without a correlated change in the other. As with high levels of the SE associated with parameter estimates, a high degree of dependency is problematic in terms of being confident about changes in 0 s delay performance and rate of forgetting as the two are confounded by the analysis. Table 3.1 indicates that in every single case, the two parameters obtained from the exponential function (*Log do* and *b*) are more independent from one another than the two parameters obtained from the hyperbolic function (*Log do* and *h*).

In summary, although both the exponential and hyperbolic functions provide very good fits to the change in *Log d* as a function of delay in the current task, the exponential function is superior in terms of its ability to produce unique and independent parameter estimates. Furthermore, use of the exponential function tends to result in more conservative estimates of parameters than does use of the hyperbolic function. Consequently, use of the exponential model is to err on the side of making a Type 2 error, whereas use of the hyperbolic model is more likely to result in a Type 1 error being committed when deciding whether a particular manipulation has had an effect. Therefore, the exponential function was used to describe performance changes in DMTS performance throughout the remainder of the research reported in Chapter 3. It should be emphasised that the choice of the exponential model was not made on the basis of any theoretical considerations of memory performance but entirely on the basis of the empirical comparison between the two models. Indeed, in other circumstances the hyperbolic model may provide a better description of data and the choice of model itself is probably not critical because both functions result in similar conclusions as a rule (e.g. Table 3.1; McCarthy & White, 1987).

Part 2

Part 2 of Experiment 3.1 assessed the effect of MS, MB and sham-control lesions on performance in the DMTS task. The results indicated that none of the surgical groups examined in Part 2 showed any change in DMTS performance pre- versus post-surgery.

After obtaining the baseline, pre-surgery performance of individual rats in Part 1, they were divided into three groups and given either a MS, MB or sham-control lesion. Histological analyses conducted several months later, after Experiment 3.3, indicated that these lesions resulted in the appropriate damage for individual rats within each group (see Appendix A). After a brief period of recovery, they were placed back into the DMTS procedure. The first 5 sessions post-surgery were treated as a period of re-familiarisation with the task and were not included in the present analysis. Data from the subsequent 20 sessions were used to compare pre- and post-surgery performance for individuals in all three groups and the group as a whole. A group function was obtained by taking the mean *Log d* for all individuals in a group at each delay and fitting Equation 1. That is, the group *Log d*s were treated the same way as individual subjects' *Log d*s. Throughout the DMTS research presented in Chapter 3 this method of calculating group *Log d*s (and hence group *Log do* and *b* values) was used because it effectively weights the contribution of each individual in the group equally and in addition the obtained parameters remain bias free. (If, alternatively, group functions were calculated by pooling the data from each subject within the group into a single stimulus-response matrix then subjects who had completed more trials would contribute more to the group function and idiosyncratic biases would tend to cancel one another, thus lowering overall group accuracy).

Figures 3.1 - 3.3 show individual and group DMTS performance pre- and post-surgery for the MS, MB and sham-control groups respectively.

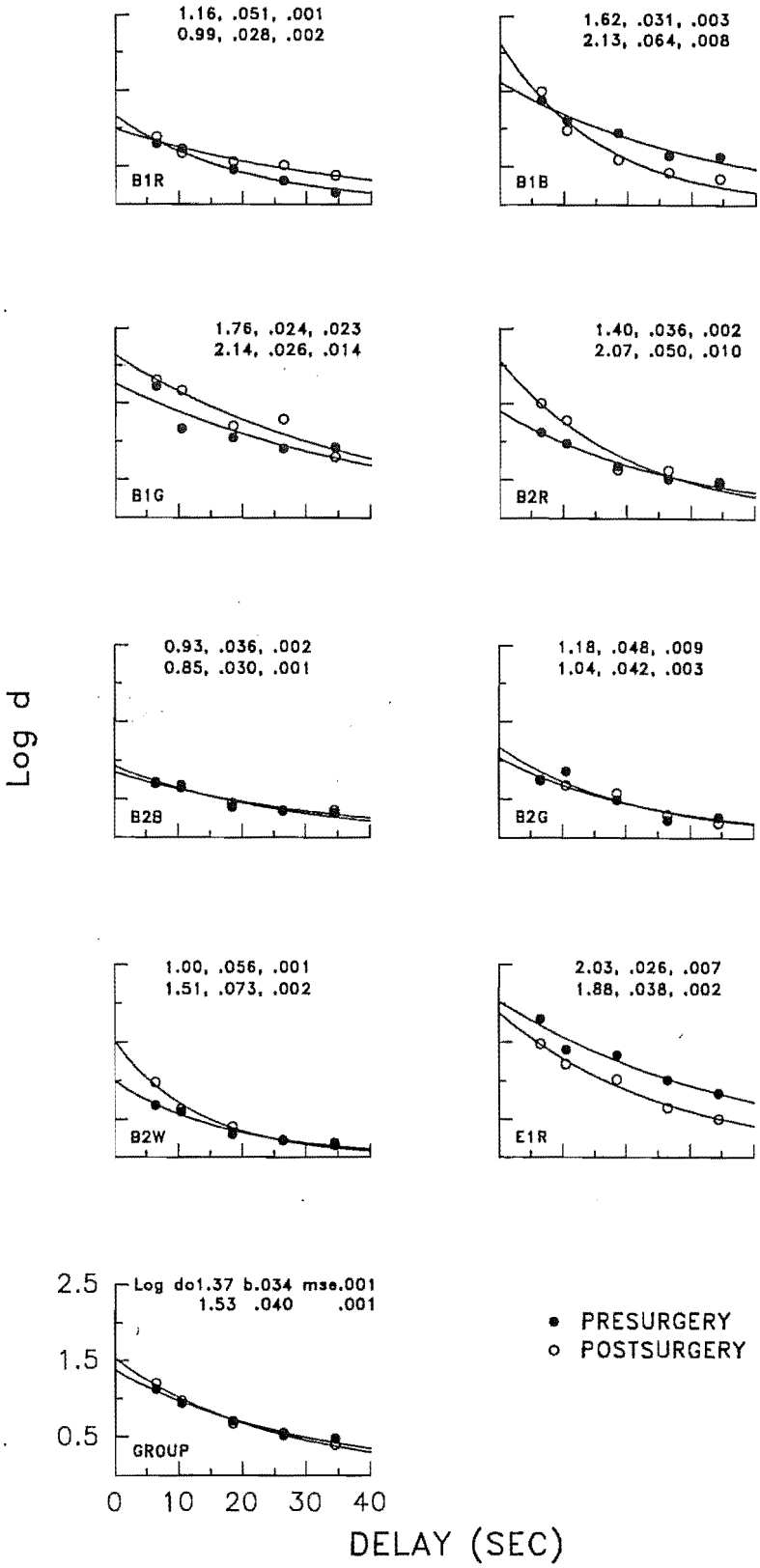

FIG 3.1 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for individual rats and the whole group prior to (filled circles) and following lesions of the MS (open circles). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*). Parameter estimates *Log do* and *b* as well as mean squared error (MSE) are shown respectively, for pre- (top line) and post-surgery (lower line).

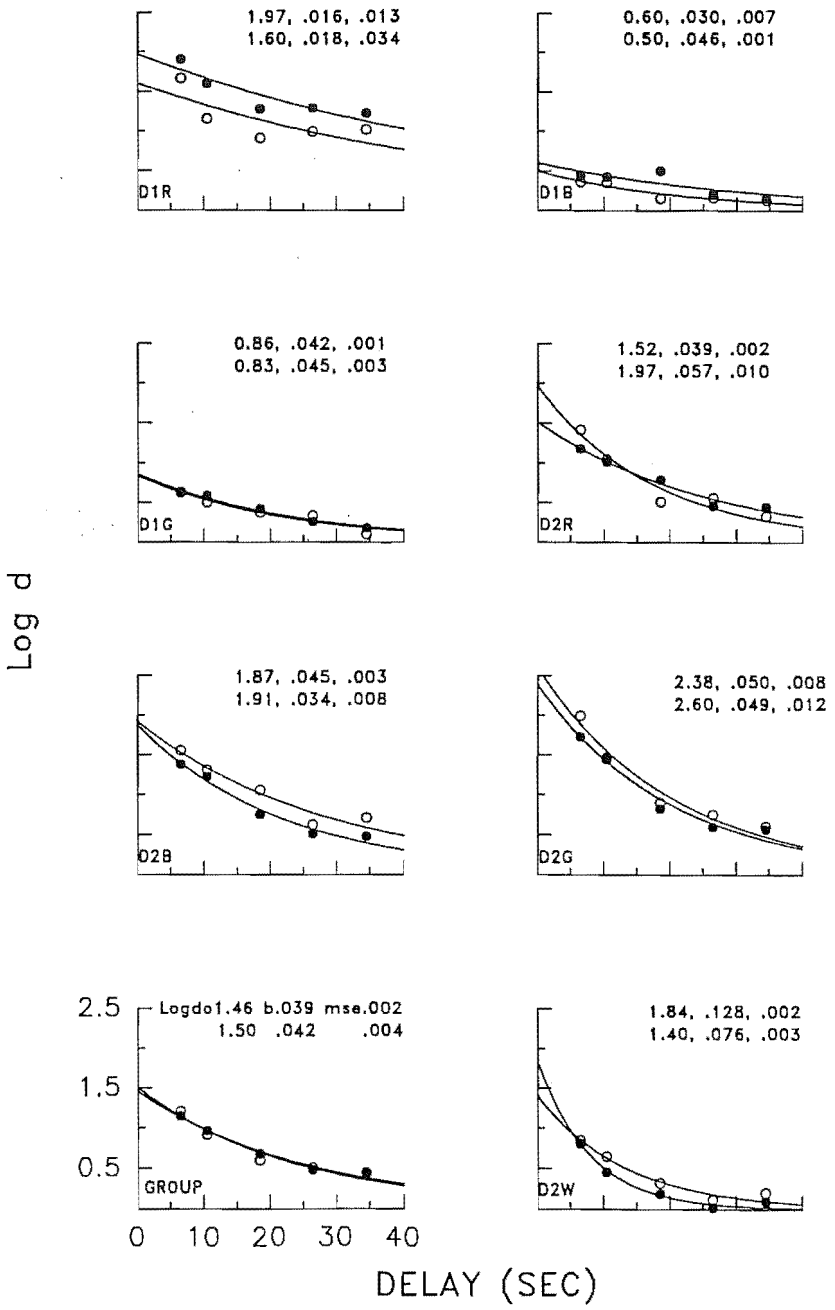

FIG 3.2 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for individual rats and the whole group prior to (filled circles) and following lesions of the MB (open circles). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*). Parameter estimates *Log do* and *b* as well as mean squared error (MSE) are shown respectively, for pre- (top line) and post-surgery (lower line).

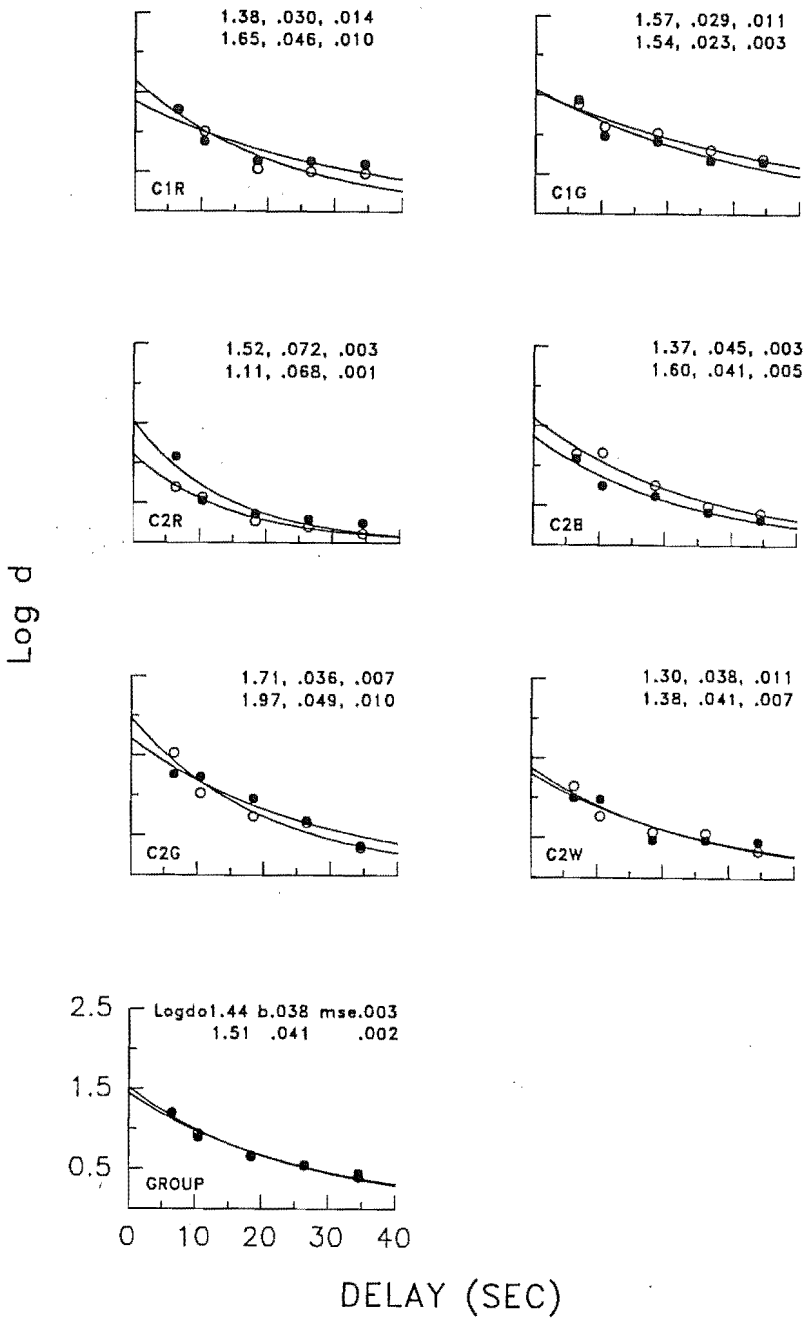

FIG 3.3 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for individual rats and the whole group prior to (filled circles) and following sham-control surgery (open circles). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*). Parameter estimates *Log do* and *b* as well as mean squared error (MSE) are shown respectively, for pre- (top line) and post-surgery (lower line).

Figures 3.1, 3.2 and 3.3 all indicate that irrespective of whether rats were given an MS or MB lesion or sham-surgery, there was no effect on basic DMTS task performance. In all 3 groups some individuals displayed a shift in the forgetting function pre versus post surgery but these changes were not consistent across the individuals within any group. The lack of change displayed by the functions themselves is reflected in the values for *Log do* and *b* obtained from each group pre versus post surgery. Across the MS, MB and sham groups, performance was very similar prior to surgery. That is *Log do* was 1.37, 1.44 and 1.46; and *b* was .0303, .0382 and .0388 for the MS, MB and sham groups respectively. Following surgery there was a slight (but statistically nonsignificant) increase in *Log do* (1.52, 1.51 and 1.50) and *b* (.0404, .0411 and .0418), for MS, MB and sham groups respectively. Consequently, a Group x Condition (pre- vs post-surgery) ANOVA, with Condition as a repeated measure revealed no effect of Group or Condition nor an interaction between them for either *Log do* or *b* ($F<1.0$). Thus, neither the delay-dependent or the delay-independent aspects of performance were altered in any systematic way in the current surgical groups.

The lack of change in DMTS performance in either the MS or MB lesioned groups is somewhat surprising given the finding that these lesions produce deficits in a variety of memory tasks (e.g. T-maze alternation, Morris Water Maze and 8-arm radial maze - see Sections 1.2 and 1.3) and both regions are implicated in the memory disruptions observed in AD and KS. The current lack of an effect on DMTS is particularly surprising for the MS-lesion group given that damage to this structure reliably produces memory deficits (e.g Rawlins & Olton, 1982; Hepler et al., 1985; Harrell et al., 1987; Harrell et al., 1983; Crutcher et al., 1983; Miyamoto et al., 1987; Olton et al., 1978; Decker et al., 1992) and caused the severe disruption to SPR observed in Experiment 2.3. With respect to the MB lesion, although some studies indicate that damage in the MB does produce memory deficits, the current lack of deficit shown by the MB-lesion group is consistent with the lack of disruption observed in maze-based DNMTS tasks, automated DMTS tasks (e.g. Aggleton et al., 1990; Aggleton et al., 1991) and the mild disruption to SPR in Experiment 2.3. Histological analyses (see Appendix A) confirmed

that the lesions were successful in producing appropriate cellular damage in the same locations as in Experiment 2.3 and that the MS lesions were successful in producing small, but observable decreases in hippocampal AChE. Furthermore, although it is not easy to compare the difficulty of two tasks, the DMTS task was probably not a great deal less challenging than the SPR task. For instance, performance in both tasks was consistently above chance levels, but neither resulted in ceiling levels of accuracy. Also, previous studies using DMTS to investigate lesion effects have shown obvious changes in performance post-surgery. For example, anterior thalamus, fimbria-fornix, and nucleus basalis damage all cause deficits in performance (Aggleton et al., 1991; Dunnett, 1985; Dunnett et al., 1989; Etherington et al., 1987). Therefore, the lack of lesion effects here did not stem from either poor lesions or insufficient difficulty of the DMTS task.

The lack of effect resulting from surgery in the DMTS task, compared with previous research may be due to many reasons. For example, studies differ in terms of amounts of training, precise lesion sites and sizes as well as the degree to which various procedures can be said to be testing memory performance as opposed to memory performance confounded by other behavioral requirements. However, the lack of impairment in the DMTS task, as compared with the impairment observed in SPR was not because of differences in the lesion sites or sizes because these were very comparable between the two studies. A possible critical difference between the SPR and DMTS tasks used in Experiments 2.3 and 3.1 is in terms of the amount of retroactive interference (i.e. the occurrence of events during the delay between stimulus presentation and recognition) and proactive interference (i.e. the occurrence of events prior to stimulus presentation) present in the two procedures. A consideration of these sources of interference gave rise to the conditions used in Part 3, to examine the interaction between lesion and interference effects in DMTS performance.

A number of studies have shown that the occurrence of events after the to-be-remembered-stimulus has been presented reduces subsequent recognition accuracy

(White, 1985). The presence of such retroactively interfering events in the SPR task, and their absence in the DMTS task, may have been critical factors in determining the presence of a memory deficit following MS lesion damage in particular. It may be that the SPR task revealed a difference between lesion groups because of the presence of high levels of retroactive interference. In the SPR task the MS group, but not the MB group, was particularly impaired for items early in the list. Presentation of these early items is obviously followed by presentation of others, which on a trial to assess memory for an early item are irrelevant for correct performance in the immediately forthcoming test phase. Therefore, MS-lesioned rats may have been more impaired at earlier serial positions compared to later ones as a product of the number of irrelevant items which followed presentation of the target stimulus. In contrast, presentation of the target stimulus on a given DMTS trial is not followed by presentation of other potential target stimuli during that trial. Thus, arranging the presence of delay events which are irrelevant to the task of remembering a particular target stimulus may be necessary to reveal an MS-lesion effect on DMTS performance. However for the MB-lesioned rats, the presentation of irrelevant events during the delay in a DMTS trial still may not reveal a performance deficit; this would be consistent with the lack of a substantial disruption observed in SPR performance in Experiment 2.3. Therefore, Part 3 examined the effect of two delay events which have been shown to be effective in disrupting operant DMTS performance with other species - turning on the houselight (White, 1985; Roberts & Grant, 1978) and delivery of a 'free' reinforcer (Jans & Catania, 1980).

As may be the case with retroactive interference, lesioned rats might be particularly susceptible to proactive sources of interference. For example, the proactively interfering effect of previous trials on later ones may have been partly or wholly responsible for the general decrease in accuracy observed across all serial positions in the SPR with MS-lesioned rats. Thus, scheduling events that proactively interfere with DMTS performance may also reveal a deficit with the MS and /or MB-lesion groups compared to controls. Stimuli and events that occur on immediately preceding trials have a disruptive influence on current trial performance when they are different from

the target stimuli in the current trial. Furthermore, it would be expected that decreasing the interval of time between trials would increase the disruption. This pattern was demonstrated by Edhouse & White (1988) using pigeons in a DMTS task in which ITI was varied from 5 to 20 s. They showed decreases in the ITI were accompanied by decreases in accuracy at each delay, reflected in a decrease in *Log do* and an increase in *b* in terms of the Exponential model. Dunnett & Martel (1990) examined DMTS rat performance at ITIs of 5, 15 and 45 s. They only found an impairment in current trial performance at an ITI of 5 s. Given that their DMTS procedure was very similar to that used here (i.e. lever position stimuli in an operant chamber), it may be that the current ITI of 15 s did not allow proactive interference to influence rat performance in Part 2 of the present experiment. Therefore, reducing the ITI to 5 s may increase interference in the DMTS task which may reveal group differences in performance - this was examined in a separate condition in Part 3.

Part 3

Part 3 of Experiment 3.1 investigated 3 disruptive conditions on DMTS performance in MS, MB and sham-control lesioned rats. The results presented below show that although interference produced a disruption to performance in terms of a delay-independent decrease in accuracy, there was no differential effects across surgical groups, nor was there any change in the rate of forgetting.

Each interference condition was run for 23-25 sessions and measures of *Log d* were taken for each delay from the last 20 sessions in the condition. In the first condition the ITI was reduced from 15 to 5 s; in the next condition, a houselight in the centre of the chamber ceiling was turned on for the middle portion of the delay; and in the final condition a free-food reinforcer was delivered immediately following stimulus presentation, but prior to rats making their choice response after the delay had ended. Figure 3.4 shows DMTS performance post-surgery and for each of the interference conditions in Part 2 for the MS, MB and sham-control groups respectively. A group function was obtained by taking the mean *Log d* for all individuals in a group at each

delay and fitting Equation 1. (That is, the group *Log d*s were treated the same way as individual subjects' *Log d*s).

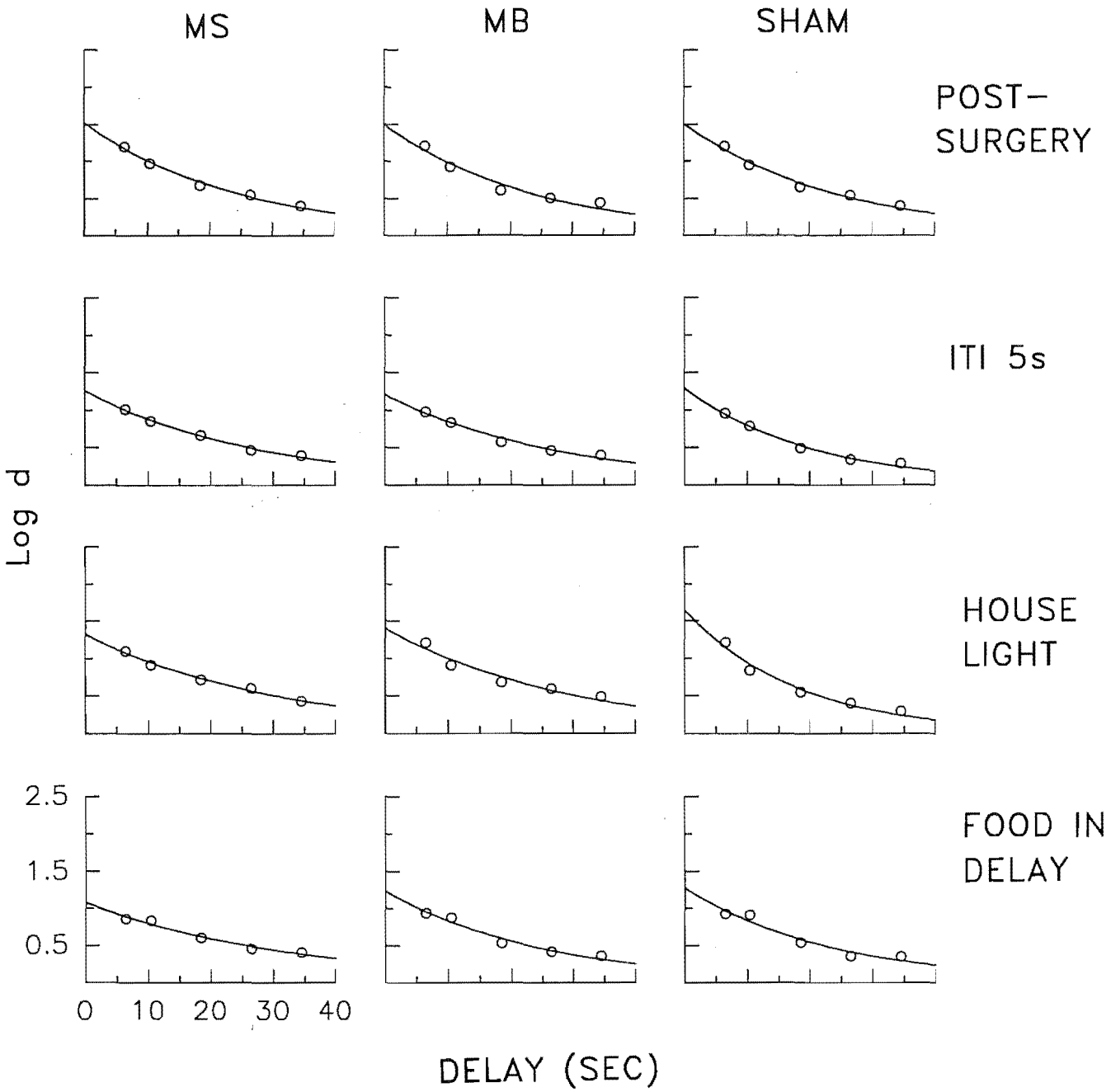

FIG 3.4 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for the MS (left column), MB (middle column) and sham group (right column)- post-surgery in the basic DMTS task from Part 1 (top graph), with the ITI equal to 5 s (second graph), the houselight operated during the delay (third graph) and with a 'free' food reinforcer delivered during the delay (lower graph). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide a measure of delay-independent performance (*Log do*) and rate of forgetting (*b*) - (these are plotted as a function of condition in FIG 3.5). Equation 1 fitted all the sets of data well with MSE typically equal to .001, with .004 being the worst fit.

Figure 3.4 indicates that in all 3 groups, across all conditions, the exponential function provided a good description of changes in accuracy (*Log d*) as a function of delay. However, it is apparent that in no case was there a large change in overall accuracy, that is the manipulations performed in Part 3 did not result in large scale disruptions to DMTS task performance. This is reflected in a nonsignificant change in accuracy over all delays as a product of either Condition or Group as revealed by an ANOVA analysis ($F<1.0$)

Figure 3.5 shows the estimates of *Log do* and *b* obtained from the group functions obtained in Part 3. Figure 3.5 indicates that there were subtle changes in performance reflected not in overall accuracy changes but changes in *Log do* as a product of condition. Changing the ITI from 15 s (during the post-surgery) to an ITI of 5 s was successful in significantly decreasing *Log do* in all three groups [$F(1,18)=12.54$, $p<.01$], but there was no effect of Group or an interaction of Group by ITI condition ($F<1.0$). A comparison of performance during post-surgery training in the basic DMTS task and the condition in which the houselight was operated indicated that *Log do* may have been reduced in the MS group, perhaps also in the MB group, and not at all altered in the sham-control group. However, although Figure 3.5 indicates that there was some separation of the groups in this condition, the absolute differences in *Log do* were not large and this was not a consistent pattern shown by individual rats. An ANOVA indicated that there were no overall effects ($F<1.0$) of either Condition (POST vs HL) or Group (MS, MB and sham) nor an interaction between them ($F=1.2$). Finally, a comparison of post-surgery performance in the basic DMTS task and the condition in which free food was presented during the delay indicated that *Log do* was reduced for all 3 groups, but slightly more so for the MS group. An ANOVA of Condition (POST vs REINF) x Group revealed a significant reduction in *Log do* [$F(1,18)=4.67$, $p<.05$] but no effect of Group or an interaction of Group by Condition ($F<1.0$). However, a separate analysis conducted for each group separately indicated that the MS groups was the only one to show a significant reduction in *Log do* when free food was presented in the delay [$F(1,7)=5.58$, $p<.05$].

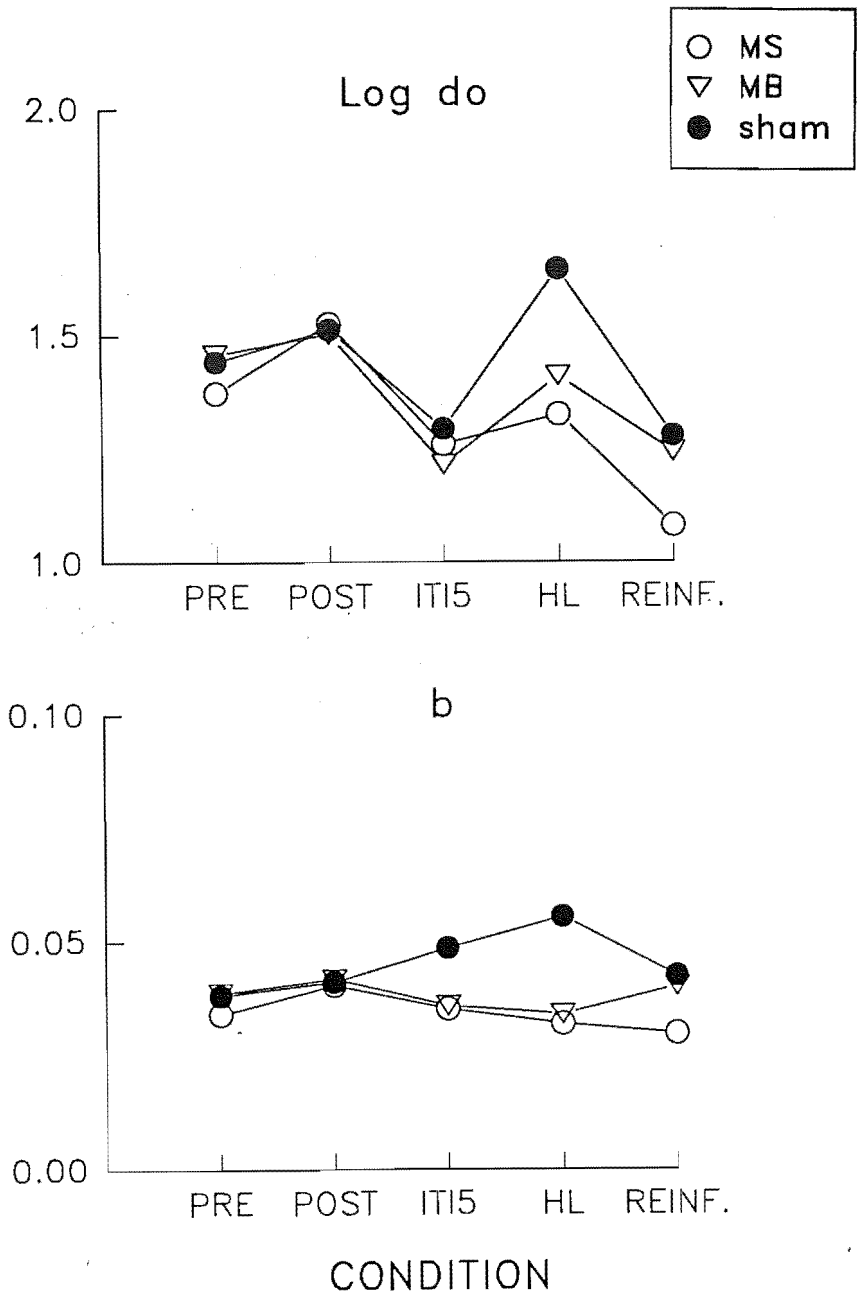

FIG 3.5 Shows changes in *Log do* (upper graph) and *b* (lower graph) as a product of condition - pre-surgery (PRE), post-surgery (POST), ITI 5 s (ITI5), houselight in delay (HL), and reinforcer in delay (REINF). These changes are shown for MS (open circles), MB (open triangles) and sham-control (filled circles) groups .

Figure 3.5 and subsequent ANOVAs showed that there was no effect of the interfering conditions on *b*. Irrespective of group, *b* did not change significantly over conditions ($F<1.0$). Figure 3.5 indicates that for the sham-control group there may have been a slightly higher value for *b* when the ITI was reduced to 5 s and the houselight was present in the delay. However, there were no statistically significant group differences in any condition and no interaction between Group and Condition for obtained values of *b*.

In summary, the results of Part 3 showed that two interference conditions were successful in decreasing *Log do* for all groups (changing the ITI from 15 to 5 s and providing a free reinforcer in the delay), and one of these conditions provided some indication that the MS group may be more disrupted than the others (reinforcer in the delay). However, in no condition was an alteration in *b* observed. Therefore, ITI 5 s and placing a reinforcer in the delay were similar in that these manipulations disrupted delay-independent performance but in no case was the actual rate of forgetting altered. The lack of a consistent effect of houselight interpolated into the delay may not be surprising given that purely visual stimuli were not a feature of the present task. Turning the houselight on in DMTS trials has previously been done with pigeons responding to key light colour (e.g. Roberts & Grant, 1978; White, 1985) and has been shown to be very disruptive to performance in these studies. A light above each lever was only one aspect of the stimulus presented to the rat on a given trial and therefore may well have not exerted a high degree of stimulus control over behavior. This would certainly be consistent with the inability of rats to learn visual operant DMTS tasks.

Despite the lack of a clear difference between groups in terms of susceptibility to interference from free food in the delay and reductions in the ITI, both these manipulations need to be examined more closely. With respect to proactive sources of interference from previous trials, it was surprising in the current study that the MS group were not affected by a reduction in the interval between trials given that in the SPR procedure they were disrupted by previous trials. Although there was no differential

effect between groups in the DMTS procedure, the reduction in *Log do* resulting from reductions in the ITI is still a promising disruptive manipulation. The effect on *Log do* here was consistent with Dunnett & Martell (1990) who showed that a reduction in the ITI from 15 to 5 s resulted in a small but consistent disruption in accuracy at each delay. Although Dunnett & Martel did not note any difference between ITI 15 and ITI 45 s, the levels of accuracy were very high and measured in percent correct, which would tend to obscure any differences between conditions. Indeed, behavioral research with pigeons has indicated that large changes in *Log do* and *b* can occur over alterations in the ITI length (Edhouse & White, 1988). Given that it may be possible to change DMTS performance more so than observed in Part 3 of the present experiment, it is worthwhile investigating performance changes over a greater range of ITIs than examined here. Perhaps the alteration of ITI from15 to 5 s in the present study was insufficient to cause a separation between lesion groups, and that a comparison of performance at ITIs of 5, 15 and 40 s may be more informative (especially when comparisons are made on the basis of a *Log d* analysis of accuracy).

A major interest in several studies which have investigated the proactively interfering effects of ITI reductions on DMTS performance has been an examination of current trial performance as a product of the stimulus or response in the immediately preceding trial (e.g. Edhouse & White, 1988; Roitblat & Harley, 1988; Dunnett & Martel, 1990). A consistent finding has been that accuracy was poorer on the current trial if the previous response or stimulus was different from the current stimulus. Furthermore, the disruptive influence of a previous trial on performance is heightened by reductions in the ITI. Indeed the analysis of the prior-trial effect in combination with ITI manipulations serves as a more sensitive investigation of proactive interference effects because it separates trials which are relatively more or less interfered with. Unfortunately, this more sensitive analysis of ITI effects was not possible with the data from Part 3 if we wish to use *Log d*. With only 20 sessions in each condition, undefined *Log d*s are likely to arise because the data is effectively halved by separating trials on the basis of events in the immediately preceding one. Many more trials per ITI

condition are therefore needed to gain sufficiently high resolution of response distributions. Because of the potential value of ITI manipulations as means to assess susceptibility to proactive interference, these considerations were taken into account in Experiment 3.2 which re-examined ITI effects on DMTS performance in lesioned subjects.

Similar to effect of ITI reductions, the delivery of a food reinforcer during the delay disrupted all groups to a small degree in terms of a decrease in the delay-independent aspects of task performance, and there were indications that the MS-lesion group was more affected than the MB-lesion of sham-control groups. However, the evidence for a separation of the groups in this condition was marginal. The extent of difference was reasonable but not large; *Log do* for the MB and sham group was 1.24 and 1.28, respectively; and for the MS group it was 1.08. Indeed, the ANOVA failed to reveal an overall group effect or an interaction of Group and Condition. The indication that reinforcers in the delay may serve as a potentially valuable method of disrupting behavior suggests that a closer look be taken at events in the delay as a means to show differential lesion effects, especially if greater levels of disruption can be arranged than achieved in the present study (see Experiment 3.3).

An increased sensitivity to the disruptive effect of food reinforcers in the delay for the MS-lesion group may serve as an explanation for why the primacy effect in SPR performance was highly disrupted in Experiment 2.3. In SPR, presentation of early items (which show the greatest recognition impairment) is followed by rats gaining access to subsequent list arms, each with a reinforcer at the end. For the sham and MB-lesion groups the interfering effects of food available in later list arms may be minimal and therefore, not show a disruption to primacy. Whereas, MS-lesioned rats may be highly susceptible to this source of interference. However, another possibility is that it may not be the delivery of the reinforcer per se that causes disruption but rather the behavior associated with it (e.g. eating). Human research has shown that AD and KS are very impaired in the Brown-Peterson task once a behavioral requirement is

placed in the delay (e.g. finger tapping, articulation or arithmetic calculations). Indeed, the more complex the task, the greater the impairment (e.g. Kinsboune & Wood, 1975; Mair et al., 1979; Flicker, 1984; Morris ,1986; Sullivan et al., 1986; Kopelman, 1991). So an important comparison is the effect of a free reinforcement delivery in the delay as opposed to a specific behavioral requirement in the delay. Accordingly, Experiment 3.3 examined the interfering effects of reinforcement and a specific behavioral requirement on DMTS performance.

Part 4

Part 4 examined the effect of a larger MS lesion than previously used in Experiments 2.3 and in Parts 2 and 3 of the current experiment. The lack of impairment shown by the relatively small MS group in Parts 2 and 3 was surprising given the consistency of MS lesions impairing performance in other procedures. Although the effect of MS damage may yet be revealed by manipulations of the interfering conditions in the DMTS procedure, another possibility exists. That is, there may be an interaction between the amount of septal damage and behavioral task being used, such that the relatively small damage caused by the MS lesion used here is not sufficient to result in a deficit in DMTS performance. Which aspects of the DMTS task result in a lack of sensitivity to MS damage are undetermined because there are many procedural differences between this task and other memory tasks. For example, DMTS performance is shaped gradually over the space of many hundreds of trials. Furthermore, unlike many manually-operated procedures, a large number of trials occur in a single session, and the result may be that performance in the present DMTS task is relatively resistant to lesion effects. For example, prior to lesioning rats in Experiment 2.3 had received approximately 500 SPR trials, whereas in the current experiment rats had received approximately 3000 - 4800 DMTS trials. The possibility that a relatively greater degree of MS damage is required to produce automated DMTS performance impairments is consistent with the observation that a fimbria-fornix lesion, despite impairing performance in the DMTS or DNMTS tasks (e.g. Dunnett, 1985; Etherington et al., 1989; Aggleton et al., 1991) does not result in the extreme

impairments often observed in manual maze-based tasks (e.g. Rawlins & Olton, 1983). Although it is not possible to reduce the amount of pre-training required for adequate DMTS performance, it may be that a larger lesion (although still specific to the MS region) will produce a DMTS performance deficit. In fact, the present lesion size is smaller than used by many researchers investigating MS lesion effects and the histological results (Appendix A) indicated that for all but one rat damage was restricted to the MS region. Therefore, in Part 4 a new group of 7 rats was trained under identical conditions to those examined in Part 2 and were subjected to a larger MS lesion after baseline performance was obtained.

Performance from the last 20 sessions pre-surgery was compared against 20 sessions of post-surgery performance (treating the first 5 post-surgery sessions as a period of refamiliarisation and thus not included in the analysis). Appendix A shows that one of the rats in the group of 7 (G1G) received damage anterior to the MS area. In this individual the damage was near the third ventricle just ventral to the triangular septal nuclei, and only very slight damage was caused to anterior portions of MS; accordingly there was no observable AChE depletion in the HF. This rat was included for comparison in Figure 3.6, but was not included as a member of the group function or purposes of analysis and was excluded from all further comparisons conducted in subsequent experiments.

Figure 3.6 shows *Log d* plotted as a function of delay for the rats in Part 4. The results showed that a slightly larger lesion (than used in Part 2 and 3) of the MS resulted in a disruption to DMTS performance in terms of an increase in rate of forgetting. Specifically, *Log do* was unchanged pre- vs post-surgery, but *b* showed a significant increase. The increase in *b* was reliable across all rats with large MS damage, that is all 6 rats (i.e. excluding G1G) showed an increase in *b* as compared to 2 out of 6 in the sham group, 4 out of 8 in the small MS-lesion group and 2 out of 7 in the MB-lesion group.

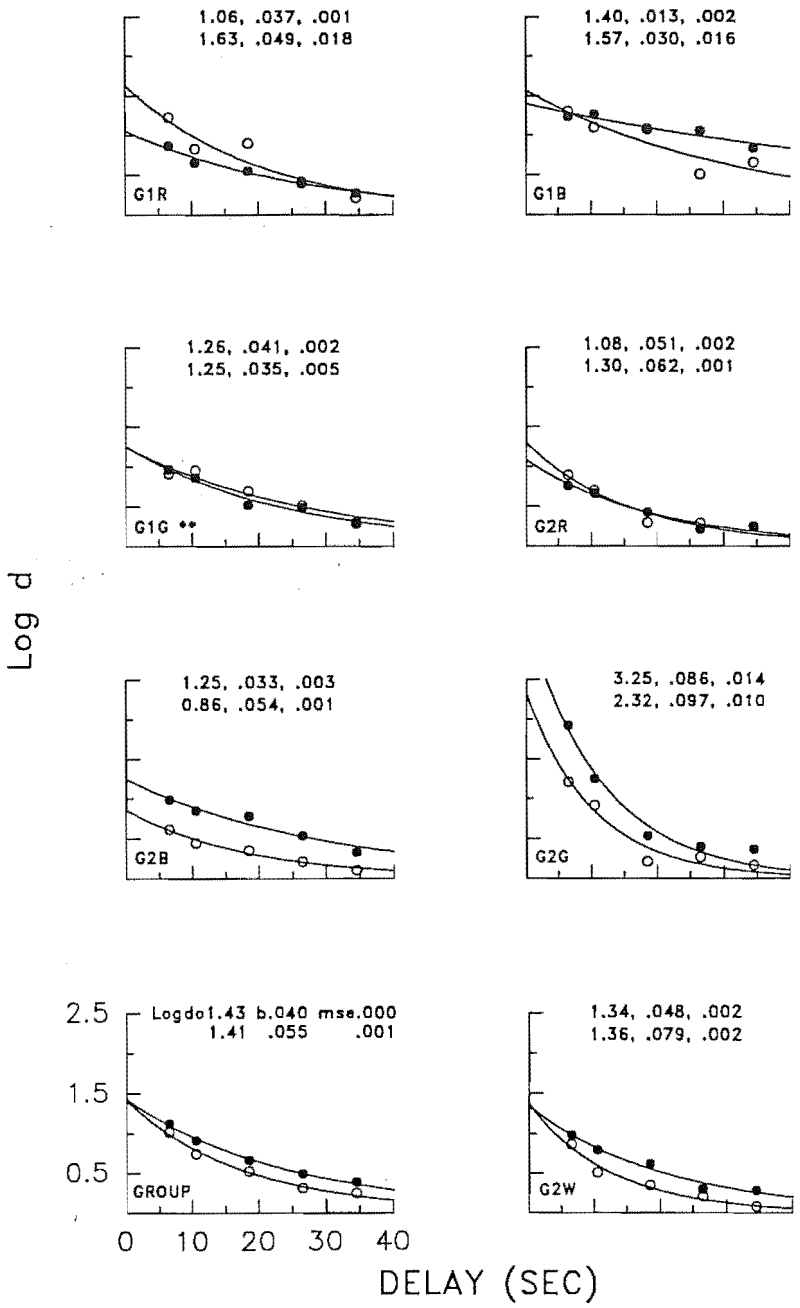

FIG 3.6 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for individual rats and the whole group prior to (filled circles) and following large lesions of the MS lesion given to 7 new rats in Part 4 (open circles). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*). Parameter estimates *Log do* and *b* as well as mean squared error (MSE) are shown respectively, for pre- (top line) and post-surgery (lower line). (**) - G1G did not display damage in the MS and is included for comparison only, also the data from this rat was not used in generating the large MS group function displayed.

A comparison of the sham-control group from Part 2 with the large MS-lesion group of Part 4, using an ANOVA with parameter estimates as repeated measures, indicated a main effect of surgery on *b* [$F(1,10)=16.32$, $p<.01$] but not on *Log do* ($F<1.0$), and an interaction between Group and surgery on the value of *b* [$F(1,10)= 8.05$, $p<.05$] but not *Log do* ($F<1.0$). Subsequent post-hoc analyses showed that the increase in *b* was significant for the larger MS group [$F(1,5)=23.64$, $p<.001$], but not for the sham-control group ($F<1.0$). This increase in forgetting (without a general delay-independent impairment) is similar to that observed those studies which have demonstrated an increase in the rate of forgetting in DMTS performance in AD and KS, both of which display neuropathology in the MS brain region (Sahakian et al., 1988; Oscar-Berman & Bonnor, 1989). This pattern of impairment observed with relatively large MS lesions also appears to be similar to the effect of fimbria-fornix lesions (which disconnect the MS and other brain regions from the HF) which cause an increase in memory decay in an automated DMTS or DNMTS tasks (e.g. Dunnett, 1985; Etherington et al., 1987; Aggleton et al., 1991). As well, the current result is similar to the effect of MS lesions on T-maze alternation after a delay between runs is imposed (e.g. Hepler et al., 1985; Thomas & Brito, 1980).

The observed effect of the larger MS lesion on *b* , and the absence of such an effect in other lesion groups, was not the product of floor effects in performance because accuracy was well above chance levels. Furthermore, the use of *Log d* to measure accuracy means that the disruptive effect of the larger MS damage was not a result of increased response bias (i.e. a tendency to favour one lever over the other). The importance of removing such bias from measures of accuracy is highlighted by plotting changes in bias pre versus post surgery. Figure 3.7 shows changes in the absolute levels of bias (i.e. ignoring bias direction) averaged across all subjects in the small MS, MB, sham and large MS groups plotted against delay. This graph and the subsequent analyses show that Log bias did not alter significantly across delays. However, over all rats there was a significant alteration in Log bias (*Log c*) pre versus post surgery [$F(3,23)=3.8$, $p<.05$] and post-hoc analyses revealed that this change was

significant ($p<.05$) for each group individually, except the MB group. Figure 3.7 shows that the pattern of bias change pre versus post surgery was different across groups. Specifically, bias increased for the small and large MS groups, decreased for the control group and was unchanged for the MB group. Thus, confounding 'nonmemorial' changes in behavior did appear to occur, and therefore this confirms that it is important to partial them out of the analysis of memory performance.

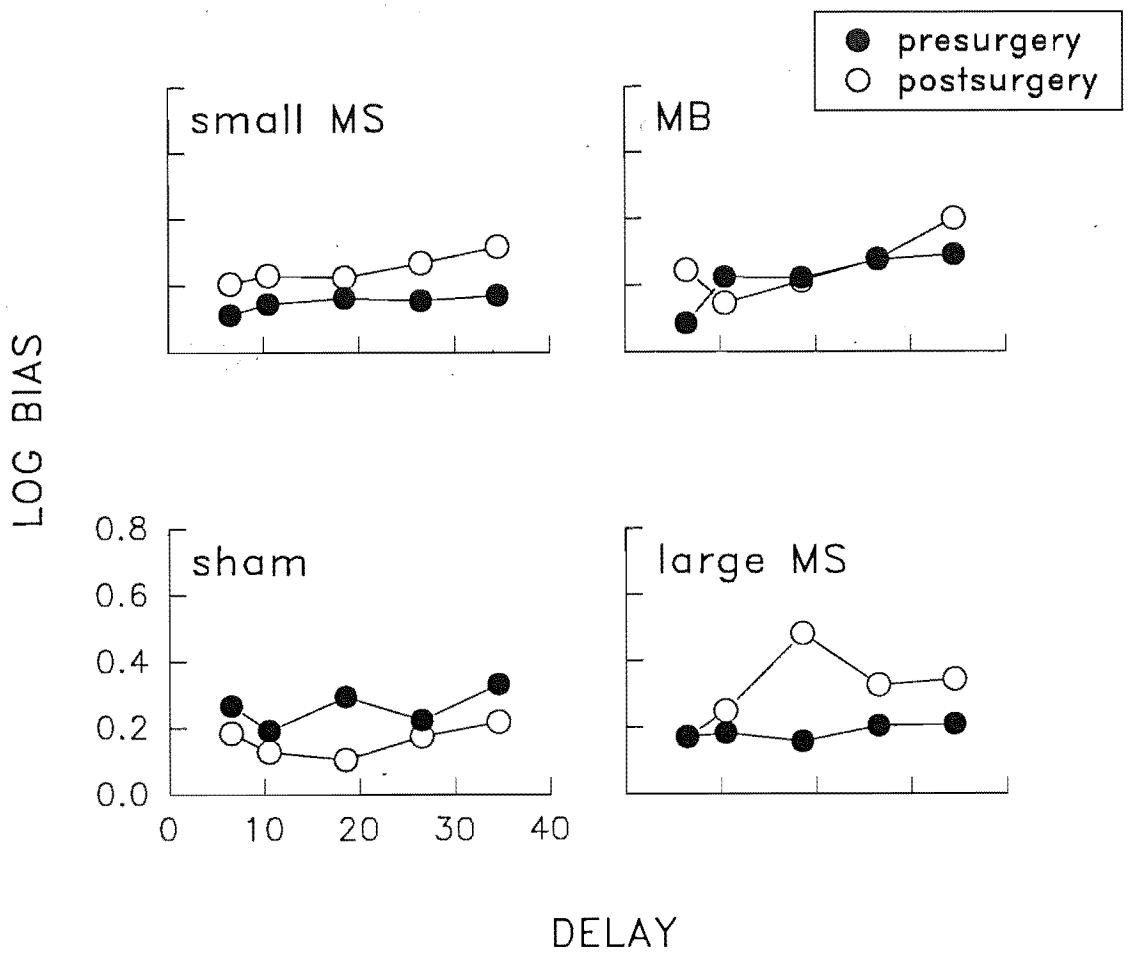

Fig 3.7 Shows response bias pre (closed circles) versus post (open circles) plotted over delays (s) for the small MS (top left), MB (top right), sham (lower left) and large MS (lower right) groups. The bias data shown were the mean absolute values shown at each delay by the individuals in the group.

SUMMARY

Taken as a whole the results of Experiment 3.1 demonstrated the utility of examining memory performance in rats using the DMTS task and the use of a quantitative model to describe performance. Rats performed in a manner consistent with other species on the basic DMTS task in that their performance was very well described by a negative-exponential function relating accuracy (measured as *Log d*) and delay. The results of Parts 2 and 3 indicated that in general there was no systematic effect of small MS or MB lesions on behavior and that there was little in the way of differential sensitivity to interference. The small MS results in particular seem inconsistent with the impairment observed in SPR performance (and in a number of other procedures) if this region plays a general role in memory. Further, these current results seem inconsistent with the possibility that MS damage may underlie the memory impairments and sensitivity to proactive and retroactive interference effects observed in AD and KS subjects. However, the results from the large MS group in Part 4 did indicate that sufficient damage in this structure may cause significant alterations in memory function.

Two manipulations (free food in the delay and ITI alterations) provided indications that they were potentially effective in altering performance in the DMTS task. Also, increasing the size of the MS lesion had a disruptive effect on performance not revealed in the relatively smaller MS-lesion group or MB-lesion group. Therefore it is important to examine these manipulations, especially in a comparison of small and large MS lesions, MB lesions and the sham-control group. So despite a lack of convincing separation between groups in conditions which schedule potentially high levels of proactive or retroactive interference this issue needs to be explored in greater depth. Experiment 3.2 was a more in-depth examination of ITI effects on DMTS performance in context of examining susceptibility to proactive interference in these lesioned groups. Experiment 3.3 was a more indepth examination of the disruptive

effects of events and behavior in the delay in order to examine more closely susceptibility to retroactive interference in the same lesioned groups.

EXPERIMENT 3.2 Lesion Effects on DMTS Performance: Influence of Proactive Interference

Experiment 3.2 was conducted in order to investigate further the relationship between lesion effects and interference in the basic DMTS task used in Experiment 3.1. The present experiment examined a more extensive variation of ITIs to manipulate levels of proactive interference using the same rats as used in Experiment 3.1. The question of susceptibility to the disruptive effects of proactive interference is of prime importance when investigating the effects of hippocampal connection damage on memory performance. There are two indications that MS damaged rats will be more susceptible to proactive interference: Firstly, human evidence from subjects with AD or KS, (both of which exhibit damage in the MS and a consequent reduction in hippocampal acetylcholine, and one of which exhibits damage to the MB), indicates that a feature of their memory disorders is an increased sensitivity to the disruptive effects of events which previously occurred (e.g. Delis et al., 1991; Kramer et al., 1988). Also, the present SPR research (Experiment 2.3) findings were consistent with the possibility that rats with MS damage may be more susceptible to the proactively interfering effects of previous trials over subsequent ones. Therefore, although the small MS lesion did not result in an impairment in DMTS performance in Experiment 3.1, it may be that by arranging conditions which are relatively more or less disruptive that group differences do emerge. In addition, rats with large MS lesions were not exposed to ITI variations in Experiment 3.1 and may display an even greater sensitivity than observed in all other groups.

There were several differences between the present study and the alteration of ITI performed in Part 3 of Experiment 3.1. Firstly in the present study, instead of just

reducing the ITI (as done in Part 3, Experiment 3.1), the interval was both decreased and increased beyond the basic length of 15 s. The advantage of altering the length of the ITI over a range of values is that patterns of behavior change may be revealed, rather than simply demonstrating that a change may occur. Furthermore, Part 3 of Experiment 3.1 indicated that a reduction of the ITI from 15 to 5 s was sufficient to cause a significant decrease in *Log do* with no difference between groups, but there are indications from previous research that performance can be altered more greatly than was observed (Dunnett & Martell, 1990; Edhouse & White, 1988). Therefore, a comparison of 5 and 40 s ITI may reveal a stronger separation between groups in their susceptibility to proactive interference. A second difference in the present study was the inclusion of the large MS-lesion group. If the extent of damage in the MS is responsible for susceptibility to proactive interference, then the larger MS-lesion group would be expected to exhibit the greatest amount of disruption.

A final difference in Experiment 3.2 compared to the previous experiment was that a more molecular analysis was used to assess the effect of proactive interference on performance. Several studies have shown that when the stimulus or response on trial n-1 is different from the stimulus presented on trial n, then performance is disrupted relative to when the stimuli or responses are the same as the current stimulus on trial n (Edhouse & White, 1988; Roitblat & Harley, 1988; Dunnett & Martel, 1990). As the ITI is decreased, these studies have also shown that the disruption to performance increases. Therefore, when investigating the effects of proactive interference on performance in lesioned rats it may be of value to examine performance on trials which differ from the immediately preceding one versus performance on trials which do not differ from the immediately preceding one. This breakdown of the data has already been employed to show the more molecular differences between aged and young rats in DMTS performance (Dunnett et al., 1990). Hence this division of performance may be informative in determining which aspects of the DMTS task contribute to the greater susceptibility to proactive interference in rats which have received lesions and may serve to reveal differential lesion effects on performance that are not readily identifiable

under a more molar investigation. Such a division of behavior means that a large number of trials have to be conducted in order to gain enough data to ensure that undefined *Log d* values do not plague the analysis. Therefore not only was ITI investigated at 5, 15 and 40 seconds duration, but also 43 sessions were conducted at each interval to allow for the molecular analysis of DMTS performance in rats.

The effect of ITI on DMTS performance is reflected in changes to both delay-independent performance and rate of forgetting. For example, Edhouse & White (1988) found that as the ITI decreased, *Log do* decreased and *b* increased when Equation 1 was fitted to their data. However, they noted that these changes to performance resulted from different aspects of the previous trial. Specifically, there was a general effect of ITI (irrespective of previous trial) on current-trial *Log do*; an affect of the prior-trial stimulus on current-trial *Log do*; and an effect of prior trial choice on current-trial *b*. It may be that susceptibility to proactive interference may occur in respect to only one or many of these sources that have previously been identified as being influential. Therefore, manipulations of the ITI combined with an analysis of previous trial influences (in terms of the exponential-decay model used in Experiment 3.1) can be used to identify not only the sources of potential proactive interferers, but also the extent of their influence on rats with MS or MB lesions.

METHOD

Subjects and *Apparatus*

The subjects and apparatus were the same as used in Experiment 3.1. That is, 4 groups of rats were tested: small MS lesion, large MS lesion (excluding G1G which did not exhibit damage in the MS region), MB lesion and the sham-control group.

Procedure

The basic DMTS task was the same as used in Experiment 3.1. However, there were 3 conditions which all rats were exposed to, for 43 sessions per condition, with only the last 40 sessions of each condition included in the analysis. Each condition was different from the others in terms of the length of the interval between trials (ITI). In the first condition rats were exposed to an ITI of 15 s, in the second condition they were exposed to an ITI of 5 s and in the final condition the ITI was 40 s. During the ITI, the chamber was in darkness. Sessions were run for 40 mins each at ITI 5 and ITI 15 s, but were run for 60 min in the ITI 40 s condition to allow for an equivalent number of trials to be conducted across conditions.

Note that one rat from the sham-control group (C2G) died after completing ITI 5 and 15 s conditions, but prior to finishing the ITI 40 s condition, and is therefore included only in the first two conditions of the current experiment.

RESULTS

Experiment 3.2 examined the effect of alterations in ITI on performance in DMTS for rats with small & large MS lesions, MB lesions and sham-controls. The results showed that ITI alterations had a number of differential effects across lesion groups at both the molar and more molecular levels of analysis. The results also indicated that the greater rate of forgetting observed with the large MS group was the result of a greater susceptibility to the disruptive effect of events (stimuli and responses) on immediately-previous trials being different from the to-be-remembered-stimulus in the current trial. The results, presented below, are divided according to an analysis of 'overall performance' (i.e. as per the prior analyses performed in Experiment 3.1, with no division of performance on the basis of events in the previous trial); an analysis of performance divided on the basis of whether the stimulus in the immediately previous trial was the same or different from the to-be-remembered-stimulus in the current trial;

and an analysis of performance divided on the basis of whether the choice response in the immediately previous trial was the same or different from the to-be-remembered-stimulus in the current trial.

Overall Performance

Figure 3.8 shows group *Log d* values (irrespective of events on the previous trial) at each delay separately for each ITI condition in Experiment 3.2. An analysis of changes in these *Log d* values as a function of delay demonstrated that the exponential function (Equation 1) provided a very good summary of DMTS performance at all ITIs for small MS, large MS, MB and sham-lesion groups. Figure 3.9 shows changes in the delay-independent performance measure (*Log do*) and changes in the rate of forgetting measure (*b*) for each group as a function of ITI.

Figure 3.9 shows that generally there was no change in *b* as a function of alterations in the ITI for any group. However, the value of *b* was consistently less in the small MS-lesion group compared to all other groups. This was confirmed by an ANOVA of Group x ITI (with ITI as a repeated measure) which indicated no effect of ITI or an interaction of ITI by Group but did reveal a main effect of Group [$F(3, 22)=3.81$, $p<.05$]. This main effect came about because the small MS-lesion group displayed a significantly lower value for *b*, irrespective of ITI, compared to each of the other groups [$F(1,22)=10.37$, $p<.01$], [$F(1,22)=4.81$, $p<.05$] and [$F(1,22)=4.25$, $p<.05$] for the large MS, MB and sham groups respectively. Therefore, although the rate of forgetting did not change as a function of ITI for any group, the small MS-lesion group was different from all others in terms of displaying a lower rate at all ITIs. The low rate of forgetting displayed by the small MS-lesion group is somewhat surprising given that it is consistently lower than obtained in all the previous conditions conducted in Experiment 3.1. It may have been that with continued training *b* decreases, however the small MS-lesion group was the only one to display such a change in *b*. Therefore, alterations in performance as a result of continued training were not a feature of most groups.

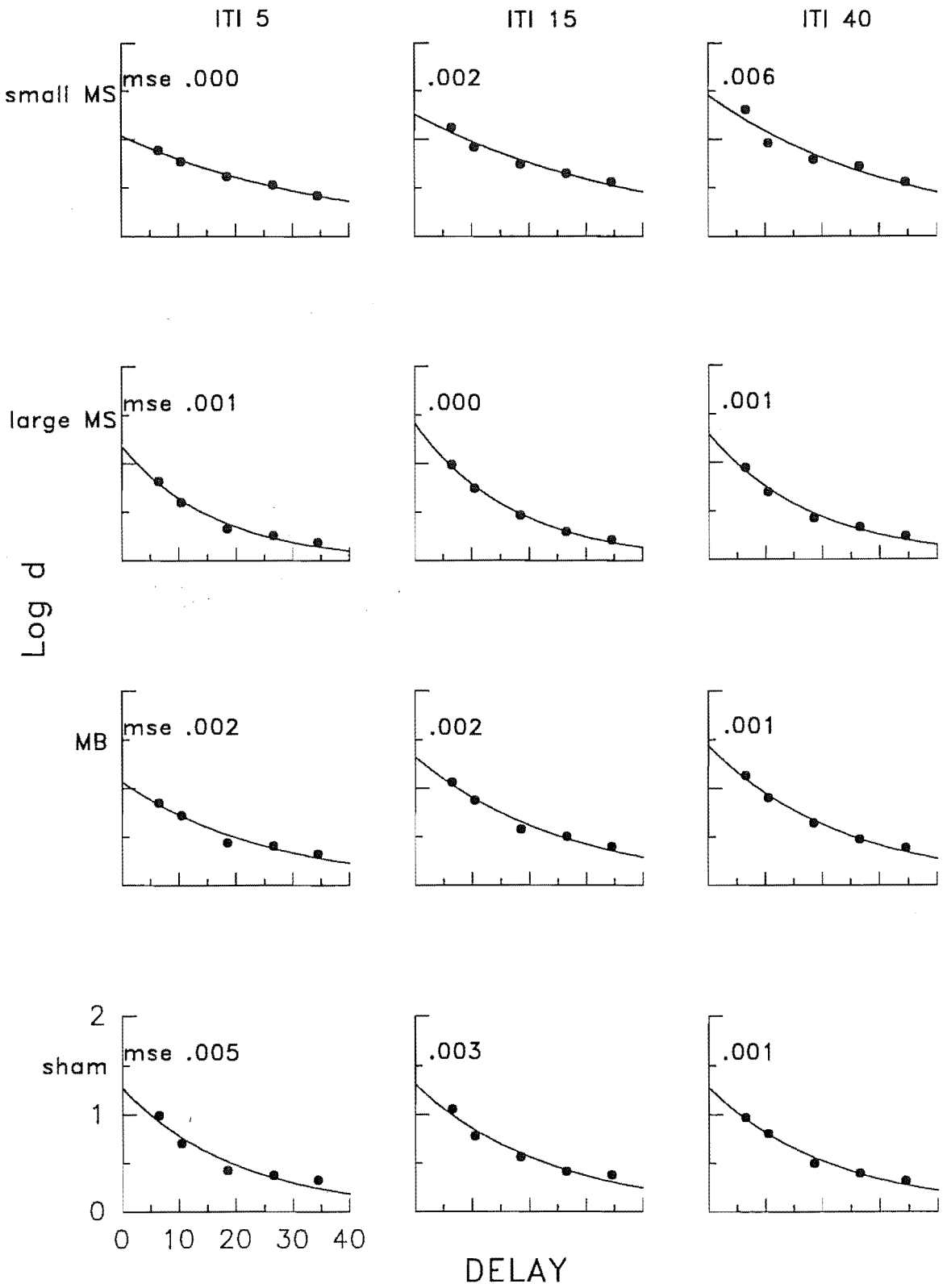

FIG 3.8 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for the small MS (top row), large MS (second row), MB (third row) and sham group (lower row) for performance in the DMTS task at an ITI of 5 (left column), 15 (middle column) and 40 s (right column). Equation 1 was fitted to these plots using nonlinear least-squares regression which provided measures of delay-independent performance (*Log do*) and rate of forgetting (*b*) - (these are plotted as a function of ITI in FIG 3.9). The mean squared error of each function fitted is given.

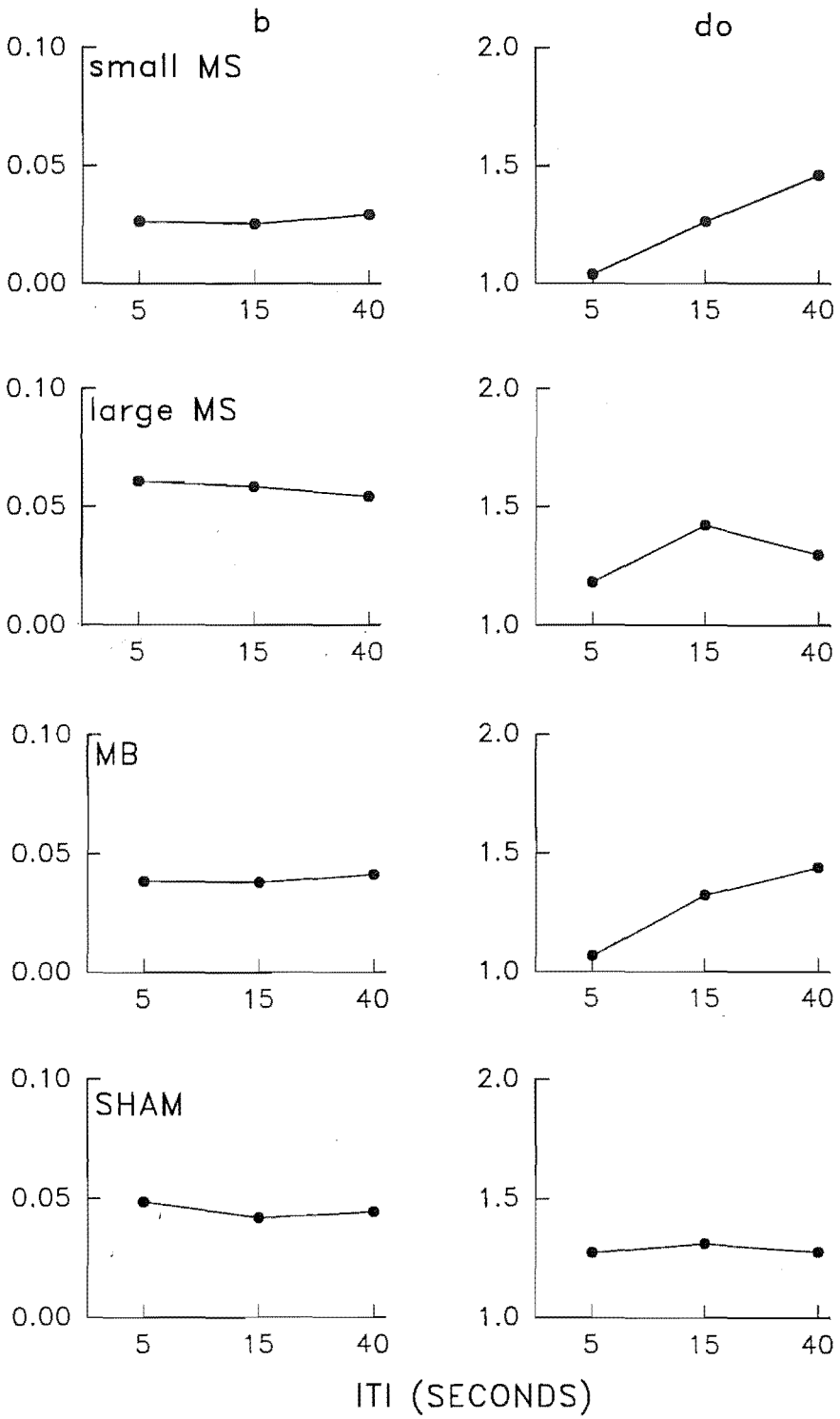

FIG 3.9 Shows changes in *b* (left column) and *Log do* (right column) as a function of ITI for the small MS (top row), large MS (second row), MB (third row) and sham groups (lower row).

As ITI was varied the values of *Log do* changed for all 3 lesion groups, but not for the sham-controls. An ANOVA of Group x ITI indicated that there was a significant main effect of ITI on the value of *Log do* [$F(2,44)=9.46$, $p<.001$] but no effect of Group ($F<1.0$) or an interaction of Group by ITI ($F=1.6$). Specifically, as ITI increased the value of *Log do* increased. This increase in *Log do* across ITI was reflected in a significant post-hoc linear trend analysis for the small MS and MB-lesion groups [$F=13.39$ and $F=9.34$, respectively, $p<.01$]. Although *Log do* did increase for the large MS-lesion group between 5 and 15 s, it did not continue to increase up to 40 s, as reflected by a significant effect of ITI on the value of *Log do* for this group [$F(2,14)=5.68$, $p<.05$] but a nonsignificant linear trend ($F<1.0$). Unlike the other groups, the sham-control group displayed no changes (linear or otherwise) in the value of *Log do* with ITI variation ($F<1.0$).

A more molecular analysis of the effects of ITI alterations on DMTS performance revealed further differences between the groups that were not obvious in the more molar analysis above. To examine the effects of previous trials on performance there are two different (although highly correlated) types of event which can be used: previous-trial stimulus, or previous-trial response. Obviously, in the 2 choice DMTS task, either the stimulus or the response in the immediately preceding trial can be the same or different from the current trial's stimulus (and hence response required to be correct in the current trial). Although trials in which the previous stimulus was the same as the previous response are highly correlated (because rats tend to get many more choices correct than wrong) these two ways to divide the data can reveal different patterns of influence on current trial performance (e.g. Edhouse & White, 1988; Roitblat & Harley, 1988; Dunnett & Martell, 1990). An analysis was conducted on the data from Experiment 3.2 in terms of both previous-trial stimulus and previous-trial response effects on current trial performance as a function of ITI, in order to explore whether any particular group (small MS, large MS, MB or sham) displayed differential sensitivity to these particular previous trial events.

Previous stimulus

Figure 3.10 shows group *Log d* values according to whether the previous-trial stimulus was the same or different from the current stimulus (i.e. the correct stimulus for the present trial) at each delay separately for each ITI condition. In Figure 3.11, the parameter (*b* and *Log do*) estimates obtained from each function fitted in Figure 3.10 are shown as a function of ITI and whether the previous stimulus was the same or different from the current one for each group of rats.

Figure 3.11 and subsequent analyses of variance clearly showed that irrespective of whether the stimulus on the previous trial was the same or different to the stimulus on the current trial, there was no effect of changes in ITI on the value of *b*. However, the group *b* values for previous-stimulus same trials were consistently lower than those obtained for previous-stimulus different. An ANOVA of ITI x previous-trial stimulus, irrespective of group, for the obtained measures of *b* revealed a significant effect of previous-trial stimulus [$F(1,25)=8.07$, $p<.01$] but no effect of ITI ($F=1.3$) nor an interaction of ITI by previous-trial stimulus ($F<1.0$). Although an ANOVA of Group x previous-trial stimulus did not reveal any significant effects of Group or an interaction of Group with previous-trial stimulus, such effects would not necessarily be expected because most subjects displayed similar trends. However, the key issue of importance is the extent to which various groups showed a different value of *b* as a function of previous-trial stimulus. Thus, a separate analysis for each group was informative with respect to determining for which groups the effect of previous-trial stimulus was significant. Indeed, an ANOVA of ITI x previous-trial stimulus for each group separately revealed that only the large MS group showed a significant effect of previous-trial stimulus [$F(1,5)=5.72$, $p<.05$] on *b*. The results in Table 3.2 also show that there was a tendency for all rats to show lower values of *b* on trials in which the previous stimulus was the same. Table 3.2 (page 177) gives individual and group *b* values according to ITI and previous-trial events (previous-stimulus same/different and previous response same/different). Specifically, comparing the *b* values for previous-stimulus same and different across all subjects and ITIs revealed that there were 21 instances (2 of which

came from large MS subjects) where previous-same *b* was greater than previous different and 59 instances (16 of which came from large MS subjects) where previous-different *b* was greater than previous same.

Figures 3.10 and 3.11 show that for all groups there was a greater value for *Log do* obtained when the previous stimulus was the same versus when it was different at ITI 5 s. But as ITI increased, the difference decreased. An ANOVA of ITI x previous stimulus effects on *Log do* revealed a significant effect of ITI [$F(2,50)=5.0$, $p<.01$] previous stimulus [$F(1,25)=6.93$, $p<.05$] and an interaction of ITI by previous stimulus [$F(2,50)=6.13$, $p<.01$]. Although an analysis of group effects did not reveal a significant difference between them, a separate analysis for each group independent of the others showed that the degree to which they conformed to the above trends differed. With respect to just the small MS and MB-lesion groups there was a significant effect of ITI on the value of *Log do* [$F(2,14)=5.86$, $p<.05$ and $F(2,12)=4.98$, $p<.05$ respectively], an effect of previous stimulus type [$F(1,7)=36.98$, $p<.001$ and $F(1,6)=10.43$, $p<.05$, respectively] and an interaction between ITI and previous stimulus type [$F(2,14)=8.29$, $p<.01$ and $F(2,12)=4.44$, $p<.05$, respectively]. The interaction between previous stimulus type and ITI for the small MS and MB groups is reflected in the results given in Table 3.3 (page 178). Table 3.3 shows the individual and group *Log do* values according to ITI and previous trial events (previous-stimulus same/different and previous response same/different). All 8 rats in the small MS group and all 7 rats in the MB group showed a lower value of *Log do* at ITI 5 s for previous-stimulus different trials compared to previous-stimulus same trials. But at ITI 40 s, 5 small MS and 4 MB rats showed a lower value of *Log do* for previous-stimulus different trials compared to previous-stimulus same trials. Specifically, the interactive effect of ITI and previous stimulus on the value of *Log do* arose in the small MS and MB-lesion groups because for both groups *Log do* from previous-stimulus different trials began at a relatively lower level and increased as a function of increasing ITI, i.e. there was a significant linear trend in the value of *Log do* from previous-stimulus different trials across increasing ITI durations [$F(1,7)=21.58$, $p<.01$; $F(1,6)=14.66$, $p<.01$, respectively]. Whereas, *Log do*

from previous-stimulus same trials did not change as a function of ITI, linear or otherwise ($F<1.0$). Thus, *Log do* values from previous-stimulus same and previous-stimulus different trials merged as the ITI increased because *Log do* from previous-stimulus different trials increased with no concurrent change in *Log do* from previous-stimulus same trials.

The sham and large MS groups displayed a pattern of change in *Log do* across ITIs visually similar to that shown by the small MS and MB groups. Figure 3.11 shows that for the sham group *Log do* was greater from trials in which the previous stimulus was the same than trials in which the previous stimulus was different and that the difference between these *Log do* values decreased as ITI increased. However, despite these trends shown in the data, an ANOVA of ITI x previous stimulus failed to show a significant effect of either variable on *Log do* for the sham group. With respect to the large MS-lesion group, Figure 3.11 shows there was only a small separation of *Log do* values at ITI 5 s according to previous stimulus type, but at ITI 15 and 40 s they displayed no separation in *Log do* values. Thus, as with sham group there was no statistically significant effect on *Log do* according to the stimulus in the previous trial, nor were there any alterations in value as a function of ITI.

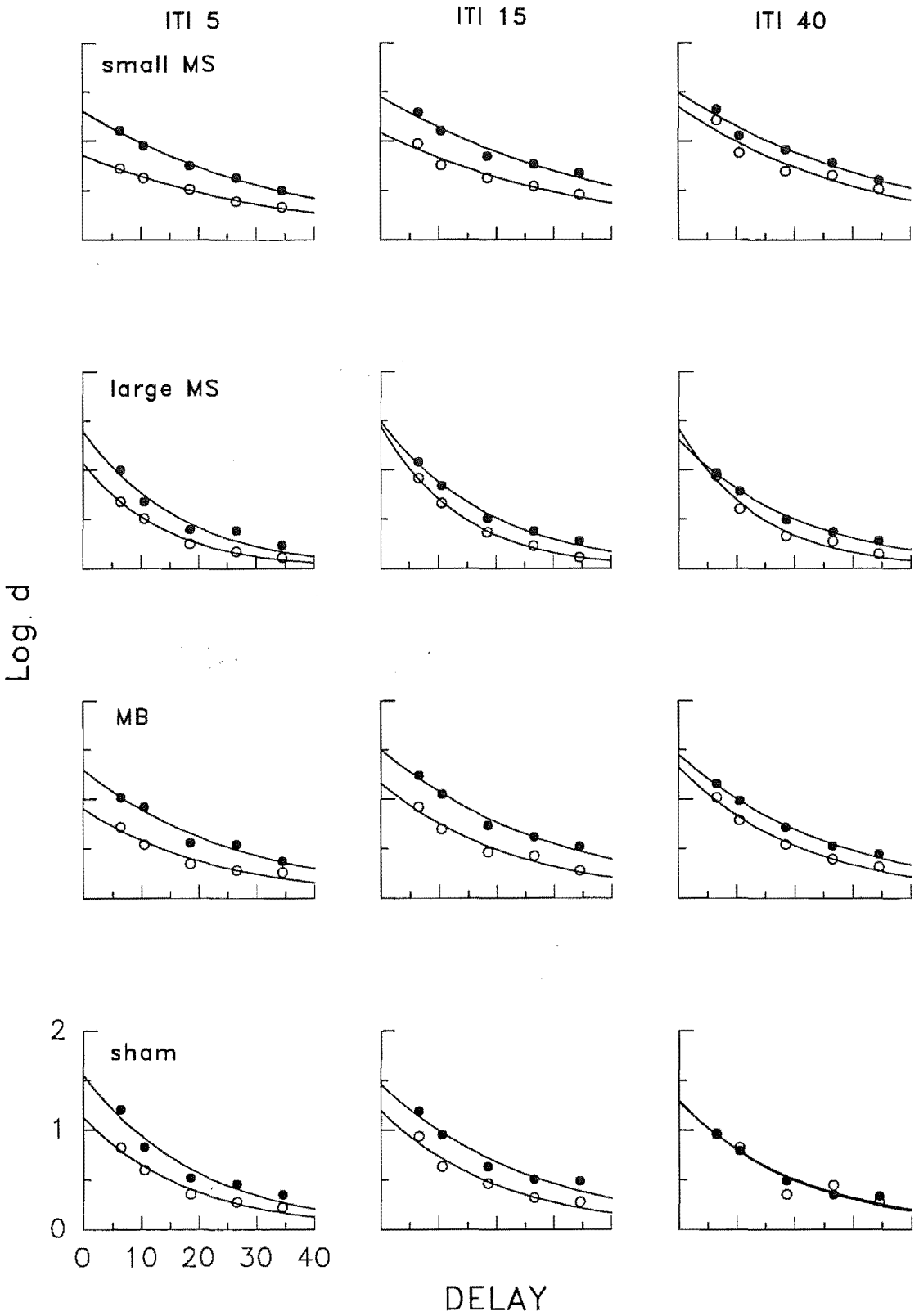

FIG 3.10 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for the small MS (top row), large MS (second row), MB (third row) and sham group (lower row) for performance in the DMTS task at an ITI of 5 (left column), 15 (middle column) and 40 s (right column). On each graph *Log d* values are plotted separately for trials in which the previous stimulus was the same (filled circles) or different (open circles) from the immediately preceding trial's stimulus. Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*) - (these are plotted as a function of ITI in FIG 3.11). The data fitted the functions well with mean squared errors ranging from .000 to .006.

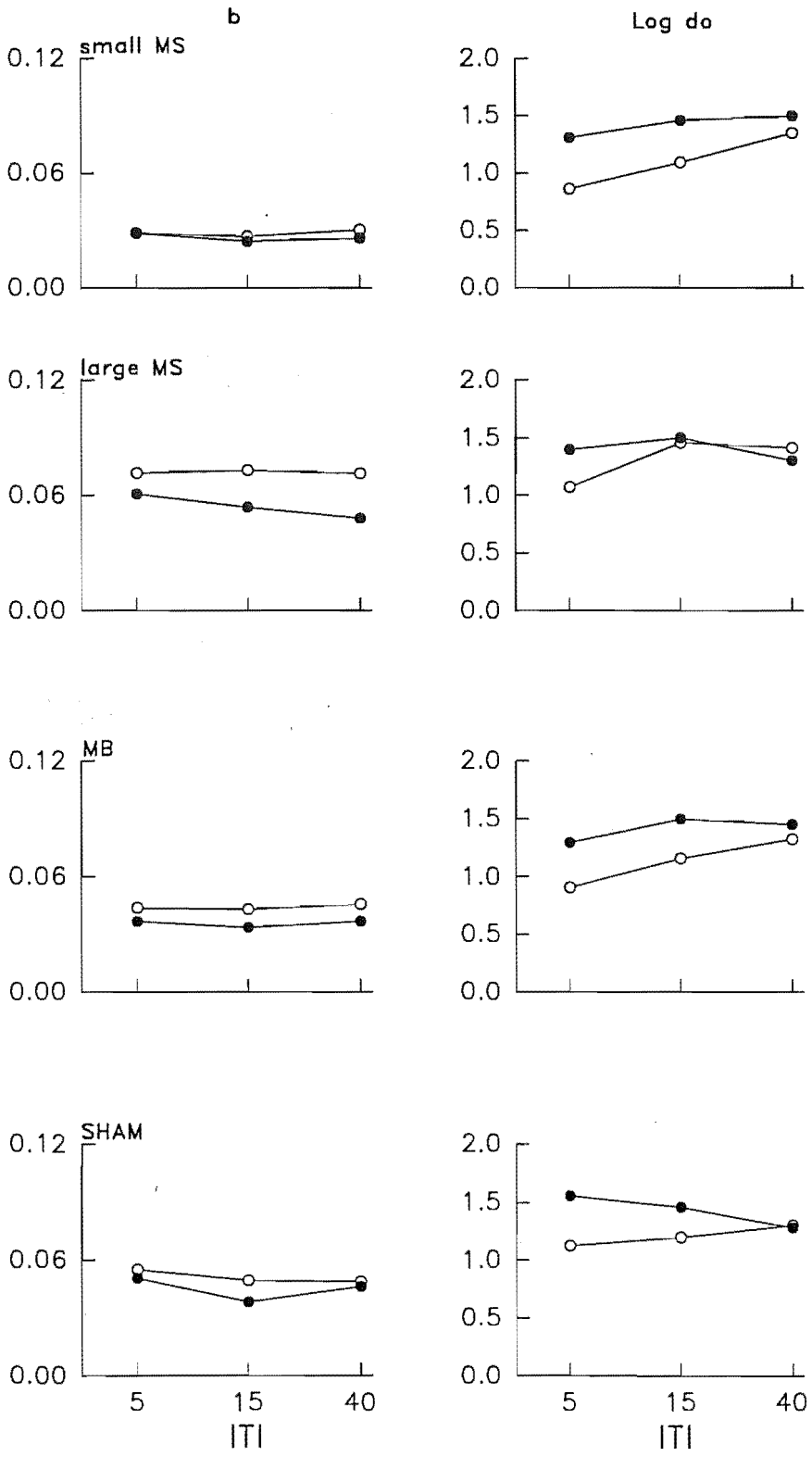

FIG 3.11 Shows changes in *b* (left column) and *Log do* (right column) as a function of ITI for the small MS (top row), large MS (second row), MB (third row) and sham groups (lower row). Filled circles are parameters obtained when the previous stimulus was the same as the current-trial stimulus, open circles are parameters obtained when the previous stimulus was different to the current-trial stimulus.

Previous response

Performance on trials in which the previous-trial response was the same or different as the current stimulus is shown in Figure 3.12. Again, group *Log d* values are plotted as a function of delay, separately for each of the surgical groups at each ITI duration. In Figure 3.13, the parameter (*b* and *Log do*) estimates obtained from each function fitted in Figure 3.12 are shown as a function of ITI for trials where the previous response was the same or different from the current stimulus for each group of rats.

Figure 3.13 and subsequent analyses of variance clearly showed that irrespective of whether the response on the previous trial was the same or different as the stimulus on the current trial, there was no effect of changes in ITI on the value of *b*. Similar to the analysis of previous stimulus effects (Figures 3.10 and 3.11), an analysis of previous response effects (Figures 3.12 and 3.13) showed that at all ITIs, values of *b* tended to be greater when previous response was different compared to when the previous response was the same as the current stimulus (and hence the same as the response required on the current trial). Table 3.2 also shows that there was a trend for all subjects to show lower values for *b* for trials in which the previous response was the same. Specifically, 21 out of all 27 rats displayed a lower value of *b* for previous-response same at all ITIs tested. Consistent with this trend in the data, an ANOVA of ITI x previous-trial response, irrespective of group, for the obtained measures of *b* revealed a significant effect of previous-trial response [$F(1,25)=17.15$, $p<.001$] but no effect of ITI ($F=1.4$) nor an interaction of ITI by previous-trial response ($F=1.6$). An ANOVA of ITI x previous-trial response for each group separately revealed that although all groups approached a significant effect of previous-trial response [$F(1,7)=4.3$, $p=.07$; $F(1,6)=4.55$, $p=.08$ and $F(1,4)=4.08$, $p=.11$ for small MS, MB and sham groups respectively] only the large MS group showed a significant effect of previous-trial response [$F(1,5)=13.09$, $p<.05$]. Indeed, ANOVAs for the large MS group alone at each ITI separately revealed a main effect of previous-trial response at each ITI - [$F(1,5)=6.79$, $p<.05$], [$F(1,5)=19.40$, $p<.01$] and [$F(1,5)=19.59$, $p<.01$] for ITI 5, 15 and 40 respectively. That is, for the large MS-lesion group the rate of forgetting is very

much greater when the previous response was different compared with when the previous response was the same as currently required, and this differentiation remained consistently large across changes in ITI.

Figures 3.12 and 3.13 indicate that for all groups there was a greater value for *Log do* obtained when the previous response was the same versus when it was different at ITI 5 s. But as ITI increased, the difference decreased. However, despite the trends seen in these figures, an ANOVA of ITI x previous response effects on *Log do*, irrespective of group, revealed only a significant effect of ITI [$F(2,50)=3.50$, $p<.05$] but no significant effect of previous response ($F<1.0$) nor an interaction of ITI by previous response ($F<1.0$). Thus, although the trends shown by the previous-response *Log do* values are similar to those obtained in the previous-stimulus analysis, there is less evidence for an interaction between previous response type and ITI.

Notwithstanding the lack of an overall interaction between previous response type and ITI on *Log do*, a separate analysis for each group independent of the others showed that the degree to which they were influenced by ITI and previous-response differed. With respect to just the small MS group there was a significant effect of ITI on the value of *Log do* [$F(2,14)=4.68$, $p<.05$], an effect of previous response type [$F(1,7)=30.44$, $p<.01$] and an interaction between ITI and previous response type [$F(2,14)=5.28$, $p<.05$]. The interaction between previous response type and ITI for the small MS group is reflected in the results given in Table 3.3. Table 3.3 shows that all 8 rats in the small MS group displayed a lower value of *Log do* at ITI 5 s for previous-response different trials compared to previous-response same trials. But at ITI 40 s, only 5 small MS rats showed a lower value of *Log do* for previous-response different trials compared to previous-response same trials. Specifically, as was the case with the previous-stimulus analysis, the interactive effect of ITI and previous response on the value of *Log do* arose in the small MS group because *Log do* from previous-response different trials began at a relatively lower level and increased as a function of increasing ITI, i.e. there was a significant linear trend in the value of *Log do* from

previous-response different trials across increasing ITI durations [$F(1,7)=19.72$, $p<.01$]. Whereas, *Log do* from previous-response same trials did not change as a function of ITI, linear or otherwise ($F=1.5$).

Figure 3.13 indicates that the sham, MB and large MS groups displayed a pattern of change in *Log do* across ITIs somewhat similar to that shown by the small MS. With respect to the sham and MB groups, Figure 3.13 shows that *Log do* was greater from trials in which the previous response was the same than trials in which the previous response was different and that the difference between these *Log do* values decreased as ITI increased. However, despite these trends shown in the data, an ANOVA of ITI x previous response failed to show a significant effect of either variable on *Log do* for either group. With respect to the large MS-lesion group, Figure 3.13 shows there was only a small separation of *Log do* values at ITI 5 s according to previous response type, but at ITI 15 and 40 s they displayed no separation in *Log do* values. Thus, as with sham and MB groups there was no statistically significant effect on *Log do* according to the response on the previous trial, nor were there any alterations in value as a function of ITI.

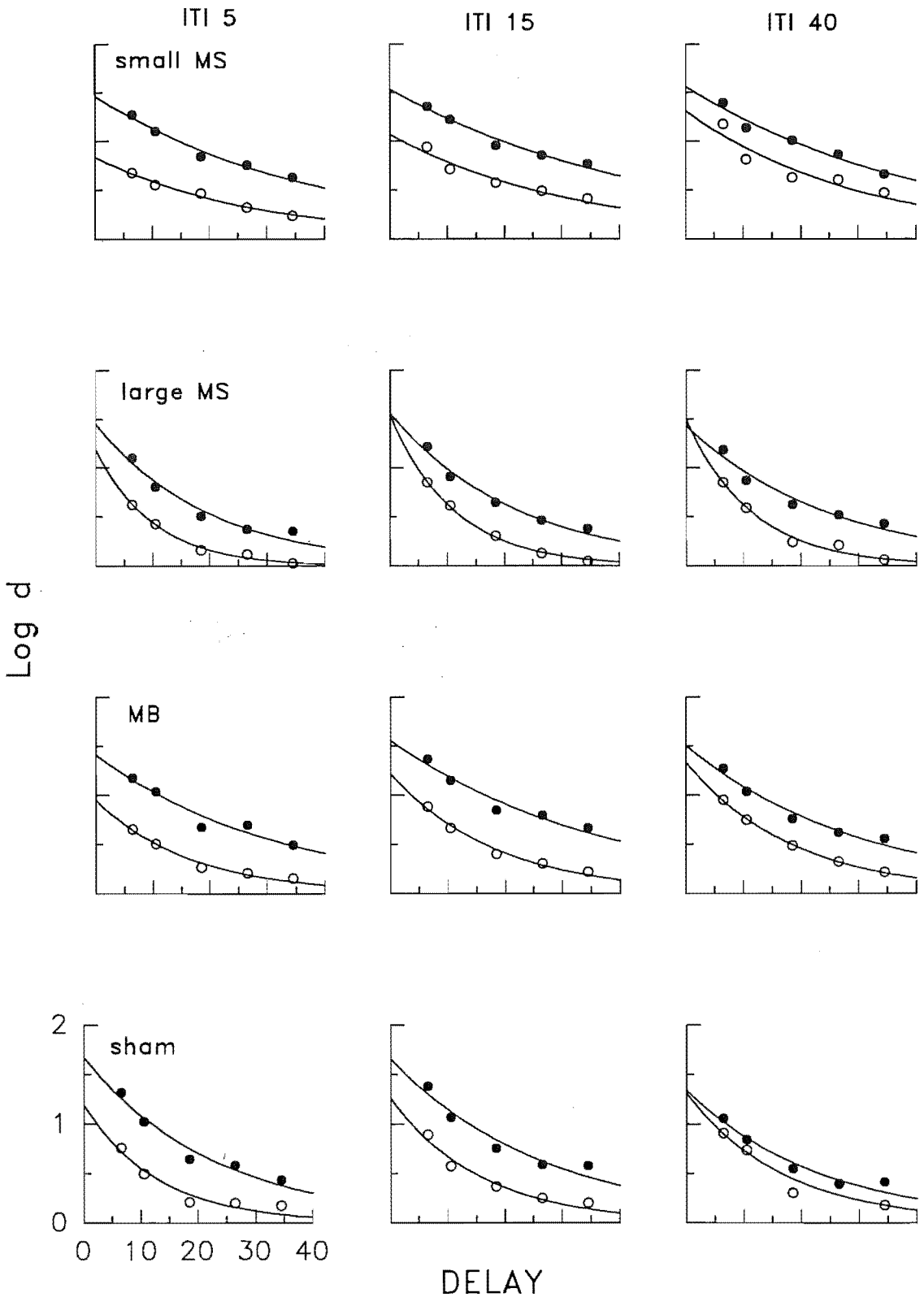

FIG 3.12 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for the small MS (top row), large MS (second row), MB (third row) and sham group (lower row) for performance in the DMTS task at an ITI of 5 (left column), 15 (middle column) and 40 s (right column). On each graph *Log d* values are plotted separately for trials in which the previous response was the same (filled circles) or different (open circles) from the immediately preceding trial's stimulus. Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*) - (these are plotted as a function of ITI in FIG 3.13). The data fitted the functions well with mean squared errors ranging from .000 to .008.

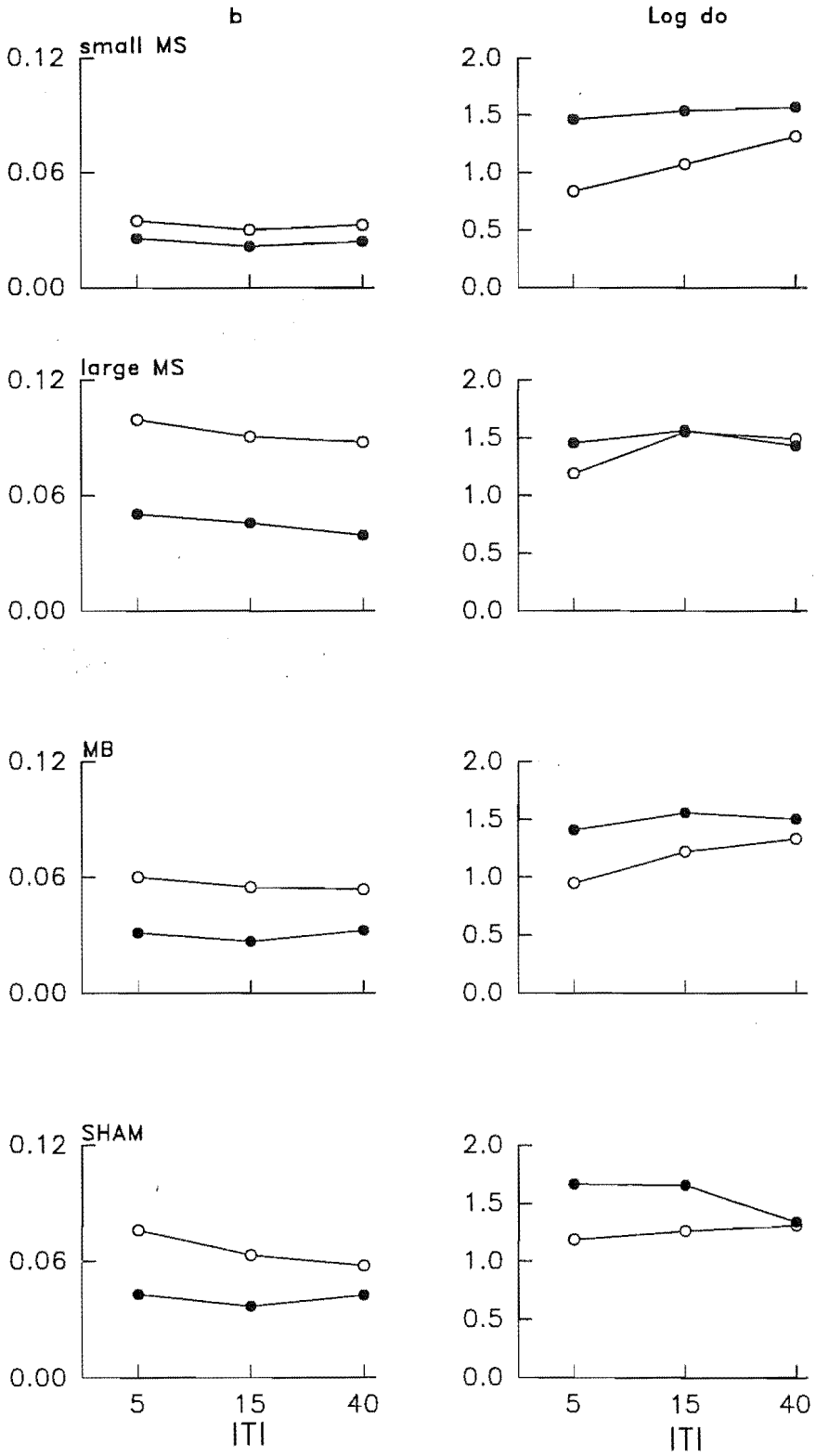

FIG 3.13 Shows changes in *b* (left column) and *Log do* (right column) as a function of ITI for the small MS (top row), large MS (second row), MB (third row) and sham groups (lower row). Filled circles are parameters obtained when the previous response was the same as the current-trial stimulus, open circles are parameters obtained when the previous response was different to the current-trial stimulus.

TABLE 3.2 *b* values for individuals and groups in Experiment 3.2. *b* values are shown for each ITI length examined and according to whether the previous stimulus (ps*) or response actually made (pr*) on the immediately preceding trial was the same (**s) or different (**d) from the current stimulus.

	ITI 5 s					ITI 15 s					ITI 40 s				
	ovl	pss	psd	prs	prd	ovl	pss	psd	prs	prd	ovl	pss	psd	prs	prd
SMALL MS LESION															
B1R	.0157	.0337	.0050	.0263	.0200	.0107	.0141	.0096	.0138	.0118	.0405	.0398	.0406	.0557	.0301
B1B	.0356	.0359	.0417	.0390	.0455	.0184	.0220	.0176	.0156	.0223	.0291	.0251	.0271	.0240	.0260
B1G	.0187	.0169	.0313	.0104	.0531	.0205	.0171	.0250	.0136	.0314	.0094	.0122	.0059	.0109	.0072
B2R	.0155	.0105	.0272	.0109	.0280	.0176	.0165	.0222	.0208	.0155	.0288	.0224	.0348	.0302	.0243
B2B	.0281	.0373	.0281	.0341	.0251	.0431	.0446	.0387	.0393	.0455	.0373	.0365	.0359	.0287	.0517
B2G	.0387	.0345	.0478	.0263	.0726	.0472	.0477	.0594	.0447	.0854	.0517	.0530	.0546	.0437	.0817
B2W	.0265	.0389	.0105	.0295	.0307	.0400	.0353	.0570	.0288	.0677	.0321	.0282	.0424	.0231	.0506
E1R	.0262	.0283	.0261	.0283	.0269	.0245	.0177	.0241	.0147	.0253	.0236	.0173	.0248	.0130	.0273
GRP	.0263	.0284	.0287	.0256	.0348	.0253	.0244	.0269	.0217	.0303	.0291	.0260	.0302	.0240	.0327
LARGE MS LESION															
G1R	.0612	.0602	.0738	.0441	.1082	.0530	.0408	.0696	.0344	.0727	.0382	.0393	.0421	.0359	.0501
G1B	.0261	.0257	.0288	.0286	.0331	.0297	.0172	.0435	.0210	.0523	.0347	.0280	.0432	.0299	.0663
G2R	.0817	.0611	.1584	.0590	.2884	.0845	.0695	.1272	.0623	.1642	.0690	.0541	.1076	.0540	.1279
G2B	.0652	.0665	.0677	.0415	.1174	.0527	.0433	.0946	.0372	.1165	.0380	.0368	.0833	.0057	.0887
G2G	.0931	.1060	.1041	.0804	.1336	.0964	.1155	.0871	.0957	.1164	.1070	.1041	.1198	.1017	.1390
G2W	.0626	.0623	.0740	.0536	.0899	.0742	.0702	.0954	.0572	.1296	.0546	.0490	.0683	.0446	.0822
GRP	.0609	.0607	.0718	.0504	.0994	.0584	.0539	.0732	.0456	.0906	.0543	.0480	.0716	.0392	.0878
MB LESION															
D1R	.0265	.0282	.0242	.0268	.0316	.0161	.0118	.0187	.0083	.0218	.0353	.0343	.0370	.0309	.0402
D1B	.0366	.0378	.0399	.0310	.0742	.0300	.0353	.0277	.0231	.0507	.0322	.0471	.0143	.0248	.0597
D1G	.0805	.1103	.0599	.0313	.2123	.0758	.0901	.0460	.0356	.1319	.0558	.0312	.0834	.0144	.1807
D2R	.0428	.0372	.0584	.0315	.0633	.0468	.0447	.0533	.0457	.0604	.0622	.0489	.0820	.0547	.0768
D2B	.0286	.0236	.0343	.0208	.0381	.0329	.0207	.0453	.0167	.0469	.0259	.0170	.0270	.0122	.0296
D2G	.0434	.0449	.0537	.0503	.0514	.0513	.0487	.0625	.0403	.0777	.0603	.0591	.0702	.0671	.0676
D2W	.0921	.1166	.1284	.0553	.2586	.1039	.0886	.2147	.0553	.3831	.0819	.0900	.1206	.0688	.2056
GRP	.0385	.0368	.0440	.0310	.0601	.0380	.0336	.0432	.0269	.0548	.0412	.0368	.0456	.0325	.0536
SHAM-CONTROL															
C1R	.0378	.0426	.0368	.0440	.0383	.0321	.0343	.0330	.0362	.0351	.0411	.0480	.0302	.0433	.0373
C1G	.0229	.0250	.0419	.0261	.0409	.0365	.0386	.0345	.0347	.0552	.0303	.0289	.0323	.0258	.0374
C2R	.1040	.0935	.2313	.0537	.2557	.0681	.0440	.1134	.0445	.1409	.0407	.0484	.1045	.0394	.2162
C2B	.0613	.0708	.0630	.0582	.0902	.0712	.0641	.0898	.0506	.1258	.0737	.0752	.0813	.0658	.1158
C2G	.0463	.0448	.0527	.0408	.0748	.0276	.0240	.0298	.0240	.0331	--	--	--	--	--
C2W	.0647	.0599	.0670	.0431	.1687	.0451	.0415	.0675	.0434	.0870	.0402	.0337	.0556	.0380	.0541
GRP	.0486	.0505	.0551	.0429	.0761	.0422	.0385	.0495	.0369	.0635	.0444	.0462	.0489	.0425	.0579

TABLE 3.3 *Log do* values for individuals and groups in Experiment 3.2. *Log do* values are shown for each ITI length examined and according to whether the previous stimulus (ps?) or response actually made (pr?) on the immediately preceding trial was the same (??s) or different (??d) from the current stimulus.

	ITI 5 s					ITI 15 s					ITI 40 s				
	ovl	pss	psd	prs	prd	ovl	pss	psd	prs	prd	ovl	pss	psd	prs	prd
SMALL MS LESION															
B1R	.60	.86	.43	.90	.45	.72	.80	.64	.92	.58	.99	.97	1.03	1.22	.87
B1B	1.54	2.04	1.25	2.60	1.24	1.51	1.98	1.26	1.89	1.30	2.54	2.55	2.23	2.54	2.10
B1G	.68	.84	.57	1.09	.52	1.16	1.46	.93	1.58	.98	1.03	1.22	.86	1.39	.79
B2R	.86	1.08	.80	1.21	.69	1.17	1.34	1.10	1.56	.93	.74	.67	.80	.88	.57
B2B	1.10	1.38	.97	1.34	.97	1.23	1.37	1.08	1.35	1.10	1.38	1.44	1.33	1.35	1.58
B2G	1.23	1.42	1.07	1.55	1.19	1.21	1.57	1.02	1.97	1.14	1.70	1.87	1.58	2.10	1.74
B2W	.51	.74	.30	.81	.30	.87	1.02	.78	.93	.91	1.14	1.21	1.13	1.17	1.20
E1R	1.86	2.26	1.61	2.38	1.56	2.37	2.23	2.12	2.23	2.05	2.39	2.35	2.11	2.25	2.17
GRP	1.04	1.31	.86	1.46	.84	1.26	1.46	1.09	1.53	1.07	1.46	1.50	1.35	1.57	1.31
LARGE MS LESION															
G1R	1.23	1.34	1.28	1.30	1.49	1.55	1.33	1.86	1.40	1.68	1.16	1.38	1.00	1.44	1.04
G1B	.87	.99	.75	1.31	.65	1.43	1.23	1.60	1.67	1.53	1.05	1.03	1.06	1.45	1.09
G2R	1.37	1.40	1.95	1.59	4.35	1.45	1.38	1.84	1.57	2.05	1.55	1.24	2.49	1.45	2.40
G2B	.75	.87	.60	.86	.72	.84	.92	.97	.98	1.01	.69	.92	.67	.87	.91
G2G	2.23	3.22	1.94	2.60	2.47	2.38	3.55	1.79	2.83	2.46	2.41	2.48	2.52	2.84	2.59
G2W	1.15	1.27	1.04	1.40	1.02	1.49	1.70	1.47	1.70	1.79	1.49	1.41	1.68	1.54	1.79
GRP	1.18	1.40	1.07	1.45	1.19	1.42	1.50	1.46	1.57	1.55	1.30	1.31	1.42	1.43	1.49
MB LESION															
D1R	1.00	1.23	.78	1.49	.73	1.38	1.50	1.26	1.57	1.24	1.68	1.84	1.55	1.79	1.60
D1B	.51	.63	.38	.77	.30	.71	.87	.56	.92	.58	.56	.72	.38	.66	.50
D1G	.76	1.01	.57	.69	1.15	1.14	1.48	.74	.95	1.44	.61	.46	.75	.58	.93
D2R	1.54	1.74	1.56	1.63	1.65	1.68	2.11	1.45	2.54	1.46	2.20	2.03	2.54	2.46	2.18
D2B	1.97	2.40	1.67	2.56	1.71	2.29	2.32	2.18	2.30	2.18	2.84	2.52	2.45	2.38	2.53
D2G	1.34	1.79	1.16	2.16	1.09	1.67	2.05	1.47	2.08	1.65	1.70	1.95	1.63	2.27	1.52
D2W	.62	.94	.56	.80	1.02	1.04	1.05	1.99	.93	5.34	.90	1.14	.96	1.09	1.62
GRP	1.07	1.29	.91	1.41	.95	1.32	1.50	1.16	1.55	1.22	1.44	1.45	1.32	1.50	1.33
SHAM-CONTROL															
C1R	1.25	1.47	1.12	1.64	1.05	1.31	1.72	1.04	2.14	.97	1.72	1.79	1.58	1.75	1.64
C1G	.92	1.02	1.00	1.26	.84	1.24	1.37	1.09	1.65	1.15	1.03	1.02	1.01	1.07	.95
C2R	1.42	1.65	2.82	1.33	1.70	1.06	.86	1.50	1.14	1.41	.70	.62	1.23	.84	1.91
C2B	1.65	2.13	1.42	1.94	1.78	1.96	2.04	2.06	1.81	2.84	2.03	2.14	2.07	2.04	2.85
C2G	1.67	2.13	1.39	2.40	1.63	1.49	1.61	1.34	1.74	1.33	--	--	--	--	--
C2W	1.22	1.45	.98	1.58	1.80	1.10	1.39	.98	1.59	1.14	1.11	1.08	1.21	1.17	1.15
GRP	1.27	1.56	1.13	1.67	1.19	1.31	1.46	1.20	1.66	1.27	1.28	1.28	1.30	1.34	1.31

DISCUSSION

An analysis of the effect of ITI alterations on DMTS performance revealed several differences between groups. In particular, a detailed analysis of previous-trial effect in combination with a manipulation of ITI duration revealed the large MS group to be dissimilar to the other groups in terms of their heightened susceptibility to proactive interference effects on the rate of forgetting. First, the extent of similarity between the small MS, MB and sham groups will be discussed. This will be followed by a comparison of these groups against the large MS group.

By and large the differences and trends in the data displayed by the small MS, MB and control groups were similar, although the degree to which such trends were confirmed by a statistical analysis varied. Furthermore, the results produced via an analysis according to previous stimulus were largely consistent with an analysis according to previous response. The main difference between these three groups was the degree to which *Log do* changed across changes in the ITI. Control rats, as opposed to small MS and MB rats, displayed very little overall alteration in delay-independent performance as ITI increased, although at a more molecular level there was a decrease in the difference between *Log do* obtained from previous different and same events (stimuli or responses). Rats with a MB or small MS lesion showed essentially the same pattern of behavior as control rats with the exception that the overall *Log do* increased as ITI increased. An investigation of previous trial influence indicated that the increase in overall *Log do* arose specifically because of the increase in *Log do* from trials in which the previous stimulus was different from the current one for both small MS and MB-lesioned rats (or in which the previous response was different for the small MS rats alone) . Consequently, because *Log do* for previous-stimulus or -response same trials did not alter over ITI changes, there was a gradual merging in the values obtained for *Log do* according to events on previous trials. Therefore, although all three groups showed a merging of *Log do* values as ITI

increased, only in the small MS and MB groups did this result in an increase in the overall value for *Log do.*

The increase in *Log do* for the small MS and MB-lesion groups that resulted from an increase of the ITI from 5 to 15 s, with no change in *b*, replicates the result found with the same subjects in Experiment 3.1 (Part 3). The present experiment showed that this was also a pattern which continued as the ITI was increased from 15 to 40 s. In contrast to Experiment 3.1 (Part 3), the control group did not show an increase in *Log do* as ITI increased. Although, the value of *Log do* for the control group at all ITI values was at least as high as the greatest value shown by the other groups. Therefore, it may have been that previous experience with alterations in the ITI and/or extensive training in the task meant that the control group was relatively resistant to the disruptive effects of ITI reductions on *Log do.* Whereas, for the lesioned animals (small MS and MB) there remained a susceptibility (in terms of the delay-independent aspects of performance) to the effect of ITI alterations on DMTS performance, although there was no difference in the degree to which the different lesioned groups appeared to be susceptible. Therefore, instead of small MS and/or MB lesions resulting in a greater level of susceptibility to proactive interference effects, it may be that both lesions result in an inability to adapt to (and hence limit the disruption from) proactive interference despite extensive experience; compared to control animals which become resistant to such disruption. Whether this was the case is uncertain because previous research has not examined the long-term consequences of training and exposure to interference in DMTS performance with rats.

The large MS-lesion group failed to show many of the trends and differences in the data observed in the other groups. Firstly, the large MS group not only failed to show a systematic change in *Log do* as ITI increased but also there was no separation of *Log do* values obtained according to whether the previous stimulus or response was the same or different from the current trials stimulus. (Although the evidence did not always support a clear separation of previous trial events in the other groups, there was

never any evidence of such a separation in the MS group - see Figures 3.11 and 3.13). Second, the large MS group was the only one to show a large and consistent difference in *b* as a product of previous events, irrespective of ITI length and irrespective of whether those previous events were stimuli or responses. Thus, a more molecular analysis of the influence of ITI alterations revealed that the major difference between the large MS-lesion group and the others was in terms of the manner in which proactive interference influenced performance in the DMTS task. That is, the small MS, MB and sham-lesion groups displayed sensitivity to the disruptive effects of previous stimuli and responses that were different to the current stimulus, but only at short ITI values and only in terms of delay-independent performance. Whereas, the large MS-lesion group displayed greater sensitivity to the disruptive effects of previous events that were different from the current stimulus, (and particularly when those previous events were responses), but only in terms of the rate of forgetting. This sensitivity displayed by the large MS-lesion group to previous-different events, in a delay-dependent fashion, suggests that this was the cause of the increased rate of forgetting observed in this group overall following surgery. That is, the increased delay-dependent sensitivity to previous-different events can account for the increased rate of forgetting observed post large MS surgery in Experiment 3.1. Part 4.

The observed susceptibility of the large MS group to proactive interference in the DMTS task is consistent with the highly disruptive effects of proactive interference in humans with MS damage (e.g. AD and KS) as well as observed susceptibility to interference from previous trials in the small MS-lesion group in terms of a general reduction in accuracy in the SPR task (Experiment 2.3). The present research suggests that the greater susceptibility to proactive interference in these other studies may have been the result of a greater forgetting rate arising from exposure to events which are different in nature from the current trial stimulus. In terms of neurological mechanisms, it may be that the increased susceptibility to proactive interference was the result of reduced hippocampal cholinergic activity following MS damage. Such a possibility is supported by the lack of obvious differences between the MB-lesion group

(a hippocampal connection, but not one which is a source of cholinergic input) and the control group. Although the results of the large MS-lesion group were consistent with the SPR research with respect to the influence of proactive interference, the small MS-lesion group in the present experiment was not. Thus, what appears to be sufficient damage (or resultant hippocampal cholinergic disruption) to cause an impairment in the SPR task may not be sufficient to cause an impairment in DMTS performance, even when the levels of proactive interference are increased in DMTS. Hence, differential levels of proactive interference across tasks are unlikely to account for the observation of a small MS-lesion effect in SPR but not in DMTS because even at very high levels (e.g. ITI 5 s) the small MS group was not differentially impaired versus other rats in DMTS.

The present investigation of ITI alterations on performance in rats using an automated DMTS procedure has implications not only for understanding the source of the increased rate of forgetting following relatively large MS damage but also the effects of proactive interference generally. For instance, the effects of proactive interference observed here with rats tended to be dissimilar to the results obtained with pigeons. Edhouse & White (1988) identified 3 sources of proactive interference using pigeon subjects: 1. an increase in *Log do* as ITI increased; 2. when the stimulus in the previous trial was different from the current one, *Log do* was lower; and 3. when the response on the previous trial was different from the current stimulus, *b* was greater, although the value of *b* for such trials was dependent on ITI (i.e. *b* decreased as ITI was increased). With respect to the first two trends seen with pigeons, the present rats either showed no overall increase in *Log do* as ITI increased (sham rats) or if overall *Log do* did increase (as with small MS and MB rats), then it was dependent upon an increase in *Log do* from previous-different trials but not previous-same trials. Thus, the difference seen between previous-stimulus same *Log do* and previous-stimulus different *Log do* was dependent upon ITI. Hence, the first two trends identified in pigeons were not independent of one another in the present rat study. Finally with respect to the last trend, to do with the interactive influence of previous response and

ITI on *b*, despite most groups consistently showing a lower rate of forgetting when the previous response was different (as per pigeons), the only group to show a statistically reliable difference was the large MS group and there were no alterations seen in the value of *b* as ITI changed. Consequently, in control and lesioned rats proactive interference acted in a manner largely dissimilar to that identified in pigeons.

The present results also appear to be somewhat dissimilar to the effects of proactive interference observed with rats in maze-based memory tasks, although there are procedural differences which make comparisons difficult. Several studies have examined proactive interference effects in rats using maze-based tasks. For example, Grant (1981) examined the proactive interference effects of prior runs on delayed alternation in the T-maze. Grant found that irrespective of whether the previous trial was same or different performance was impaired relative to a trial which was not preceded by another. This interference from a previous trial was reduced by increasing the span of time between trials (ITI). Also, the amount of disruption that arose from a previous trial was greater at longer retention intervals (40 s) relative to shorter ones (0s) an effect also observed by Roberts & Dale (1981) in the 'working memory' paradigm with an 8-arm radial maze procedure. Thus, in these two studies an increased rate of forgetting occurred as a result of the influence of proactive sources of interference, particularly at short ITIs. Their findings are inconsistent with the present findings because in the present study whether the event was the same or different from the current trial's stimulus was important in the rate of forgetting shown for all groups (although only statistically so for the large MS group).

However, the differential effect of previous-same or -different events observed in the present study is consistent with the results of other studies using maze and automated DMTS procedures with pigeons and rats (Roitblat & Harley, 1988; Edhouse & White, 1988; Grant, 1975; Dunnett & Martell, 1990). Thus, it is unclear how similar the action of proactive interference was in the present study (and indeed other DMTS-based procedures) compared with the action of proactive interference found in the

maze-based procedures used by Grant (1981) and Roberts & Dale (1981). A possible reason for the discrepancy may lie in the fact that the alternation and 8-arm maze tasks used by these authors involved responding to stimuli which are both 'to-be-remembered' and 'to-be-avoided' in any given trial, that is a target trial is preceded by both a previous-same and previous-different event. For example in the T-maze alternation task, on any trial that a rat gets correct it is exposed, and responds to, both the left and right stimuli. Therefore in such procedures while there may be an influence of previous trials on performance on current ones, there will be no differential effect of these previous trials because of the of the joint occurrence of same and different events.

The above discussion indicated that previous research with pigeons in DMTS tasks and many maze-based memory procedures with rats appears to yield results dissimilar to those observed here with respect to the influence of proactive interference. A better comparison with the present results are the findings of other studies investigating DMTS performance in rats. Unfortunately, such a comparison is complicated by the lack of systematic investigations of ITI effects on DMTS performance in rats. The most relevant study was conducted by Dunnett & Martell (1990). They investigated the effect of previous stimulus on DMTS performance in rats at ITI values of 5, 15 and 45 s, and separated the effect of previous stimulus or response on DMTS performance at ITI 5 s. Some of the trends present in their results were largely in accordance with what was observed here for the small MS, MB and control groups. For example, performance was worse when the previous stimulus was different from the current stimulus, although this was only the case at ITI 5 s; at longer ITIs there was no effect of previous stimulus. Furthermore, an analysis of previous response revealed a greater influence of previous events on performance than an analysis according to previous stimulus. That is, there was a greater separation between previous-same versus previous-different trials according to response rather than according to stimulus. However, the data presented by Dunnett & Martell (1990) do not allow for a number of the comparisons made in the present study and that of Edhouse & White (1988). ITI effects are presented on one

graph for all ITI values (making it somewhat hard to discern the performance in different conditions) and data are separated only according to previous-same or previous-different stimulus trials. Therefore, the effect of ITI on overall performance is not clear, nor is the effect of previous response according to ITI able to be discerned. Furthermore, at the shortest delay used (0 s), performance is inevitably 100% and this does not allow for accurate conclusions to be drawn regards differences in performance that may arise because of a difference in the rate of forgetting or in terms of a delay-independent performance difference. (Although, ignoring performance at the 0 s delay does suggest that there was a general delay-independent decrease in accuracy for previous-different trials c.f. previous-same trials). However, by and large Dunnett & Martell's results indicate that, as in the present study, ITI alterations produce only modest changes in overall DMTS performance, and that performance is worse for trials in which the previous stimulus or response is different from the current trial's stimulus (though only at short ITIs). The present results expanded upon these generalisations by examining the alterations that occurred in rate of forgetting and delay-independent performance as a product of ITI and/or previous event type.

In conclusion, it appears that the various sources of proactive interference (a general ITI effect and the influence of previous-trial stimulus and response on *Log do* and *b*, respectively) identified with pigeons have either a dissimilar or only a mild influence in rats, at least over the range of ITIs examined here. The present results are however, largely compatible with the existing research conducted with rats, as far as such comparisons are possible due to methodological and analytical differences between procedures. With respect to an interaction of the observed proactive interference effects and lesions, there was very little to distinguish the small MS, MB and sham groups from one another. As suggested above there was some indication that the small MS and MB groups may have remained slightly more susceptible to the disruptive effects of proactive interference on the delay-independent aspects of performance as training progressed by comparison to the control group. The most obvious group difference to emerge was the large MS group versus the rest. While the

influence of proactive interference in the small MS, MB and control groups was largely manifest in alterations to the delay-independent aspects of performance, the large MS group showed virtually no influence of ITI or previous event on these aspects. In contrast the rate of forgetting in the large MS group was highly influenced by proactive interference arising from previous trials containing different stimuli or responses. As will be discussed in greater detail in Chapter 4, these effects of proactive interference in the large MS group provide a possible mechanism by which to account for the memory disruptions observed following MS damage.

EXPERIMENT 3.3 Lesion Effects on DMTS Performance: Influence of Retroactive Interferers

Experiment 3.3 examined the effect of disruptive events which occur during the delay on DMTS performance in rats with MS, MB and sham lesions. The disruptive effects of events during the delay of a memory task are viewed as being retroactive in the sense that their influence works at a point in time after stimulus presentation but prior to recall or recognition. As with an examination of proactive interference effects, the examination of retroactive interference effects is an important aspect of determining lesion effects on memory performance. Because proactive interference appeared to act in a manner consistent with the greater rate of forgetting in the large MS group (Experiment 3.2), it may be that retroactive sources of interference may also be informative as to the causes of performance differences between lesion groups. For example, research using humans with AD or KS (who show damage in the MS with a concurrent disruption of hippocampal cholinergic activity) shows that arranging an event or behavioral requirement during the delay between presentation of a 'to-be-remembered' stimulus and subsequent recall or recognition has a particularly severe disruptive influence on these groups compared to controls (e.g. Morris, 1986; Sullivan et al.,1986). Given that sources of retroactive interference are continually present to some degree or another, it may be that differential lesion effects will arise because of differential susceptibilities to such influence. Furthermore, whereas heightened sensitivity to proactive interference appeared to be responsible for a general decrease in accuracy across all serial positions following MS damage in SPR, heightened sensitivity to retroactive interference is a possible reason for the inability of MS-lesioned rats to remember items early in a list. That is, MS-lesioned rats in Experiment 2.3 may have been unable to remember early list items because of subsequent events (stimuli, reinforcers or behavior) occurring later in the list on any given trial.

The current experiment investigated retroactive interference effects in lesioned rats and was divided into two parts. Part 1 examined the effect of altering the location in the

delay of free food delivery in small MS, large MS, MB and sham-control groups. In Experiment 3.1 (Part 3), free food was delivered only at the very beginning of the delay and the large MS group was not investigated. The other three groups which were examined showed a tendency to be impaired in terms of a reduction in performance at the 0 s delay (reflected in a reduction of *Log do*), but rats with small MS damage displayed the greatest disruption. However, in general the influence of food in the delay was weak. Furthermore, the effect of delay food on *Log do* was surprising because previous research with pigeons indicated that *Log do* would be unaffected and *b* (rate of forgetting) would increase (Jans & Catania, 1980; White, 1985). Consequently, because free food reinforcers during the delay may yet reveal convincing group differences in terms of a sensitivity to retroactive interference, and the effect of this manipulation had an unexpected effect in all groups, this issue merits further examination with all groups including the large MS group.

A critical difference between Experiment 3.1 (Part 3) and previous research examining the effect of delay food on DMTS performance may be <u>when</u> precisely in the delay food is made available. Previous research suggests that events such as food presentation in the delay clearly increases forgetting rates in pigeons (e.g. Jans & Catania, 1980) or can severely disrupt rat performance in a maze task (e.g. the effect of free access to chocolate on the recency effect in the SPR task used in Experiment 2.2). However, in previous studies, food was presented for the entire delay and the effect of altering when food is delivered during the delay has not been investigated. Because in Experiment 3.1 (Part 3) the food was presented only at the beginning and not the entire delay, it may be that the particular time in the delay that food is made available is critical in determining firstly, the degree of influence from food in the delay on DMTS performance; and/or second, an effect on the rate of forgetting rather than delay-independent aspects of performance. Specifically, in previous studies delivery of food throughout the delay means that food is available not only at the beginning but also at the end of each delay. Therefore, perhaps the occurrence of food at the end of

each delay was the critical factor bringing about sizeable disruptions to performance in terms of an increase in the rate of forgetting in these studies.

The effect of food location in the delay on DMTS performance has not been investigated to date. The only research to investigate the effect of interference location in the delay on DMTS performance has used houselight stimuli. Maki et al. (1977) examined DMTS performance in pigeons using red and green colour stimuli. During the delay, the houselight was turned on for the first 2 s, last 2 s or the complete delay. They found that delay illumination reduced performance in DMTS, but that location of the houselight had very little effect on that reduction. Rather, the amount of the delay filled with illumination was the critical factor - the greater the period of time the houselight was on, the greater the disruption. However, the effects of the temporal location of interferers on rate of forgetting is not readily obvious because a range of delays was not examined within subjects. Although alterations in houselight position during a DMTS trial has received some attention, the effect of varying when food delivery occurs in the delay on DMTS performance has not been investigated. It is difficult to extrapolate from studies exploring houselight location effects on pigeon memory performance to predictions about the effects of reinforcers in the delay on rat DMTS performance. As shown in Experiments 3.1 and 3.2, rats may exhibit differences from pigeons in terms of susceptibility to interference. Furthermore, although a number of authors have claimed that memory for arms in various radial-maze tasks is particularly resistant to retroactive interference (e.g. Maki, Brokofsky & Berg, 1979; Roberts, 1981), the effect of retroactive interference in the current automated DMTS task has only been previously investigated in Experiment 3.1. Given that pigeons display greater sensitivity to retroactive interference in operant versions of DMTS tasks as opposed to T-maze versions (e.g. White, 1985 c.f. Olson & Maki, 1983), it is important to examine more closely the effects of retroactive interference in the current automated DMTS task for rats, especially if the location of that interference has implications for the value of *Log do* and/or *b*. Hence, the question of interest in

Part 1 of the present study was, 'what is the effect of varying the location of delay disruption on *Log do* and *b* in rats with small MS, large MS, MB or sham lesions?'.

Whereas Part 1 of the present experiment examined the effect of an event interpolated in the delay, Part 2 examined the effect of a specific behavioral requirement in the delay on DMTS performance. The use of behavioral requirements during the delay has in fact been a very important feature of many theories and studies of human memory. For example, the use of a behavioral requirement in the delay is a standard component of the Brown-Peterson task. As indicated in Section 1.1.1 and Experiment 3.1, the Brown-Peterson task has been influential in determining the nature of the memory disruptions exhibited by AD and KS subjects. These subjects show a severe impairment in performance relative to controls when required to perform even very simple tasks during the delay prior to recall. These two subject groups show damage in the MS and the KS group also displays damage in the MB. Thus, the arrangement of specific behavioral requirements may be very effective in revealing MS or MB lesion effects on DMTS performance in rats.

Part 2 investigated a delay 'event' not normally used with animal subjects - that is a specific behavioral requirement. Often, nonhuman subjects are passively exposed to interfering events during the delay, for example turning on the houselight. Even delivery of free food can be viewed in this way because these events occur irrespective of an animal's behavior. However, obviously 'what' the subject does in the delay can influence performance. For example, allowing human subjects to rehearse or requiring them to perform an arithmetic task are respectively facilitative and disruptive. Previous research with rats has examined the potentially retroactive interference that may arise from being exposed to an alternate maze during a delay period. For example, Roberts (1981) examined the effect of requiring rats to run down 4 arms of 1, 2 or 3 extraneous mazes during the delay period of an 8-arm maze task. They noted that with increasing numbers of interpolated mazes into the delay (controlling for differences in the time required to complete each maze) there was a greater disruption to memory for the

arms originally presented. Therefore, one interpretation of these results is that requiring a sufficiently demanding activity of the rat during the delay will disrupt even robust memory performance. However, there are a number of questions that remain in the interpretation of these results. Firstly, Roberts (1981) did not examine a range of delays and thus the effects of extraneous maze exposure in the delay on rate of forgetting and delay-independent measures of performance are not known. Secondly, the use of extraneous mazes during the delay changes not only the behavioral requirement during the delay but also exposes the rat to very different stimuli. Such changes in the stimuli during the delay mean that a delay task such as extraneous maze exposure is not the same as the behavioral requirements often demanded of human subjects during the delay (e.g. finger tapping or arithmetic) which require no introduction of new stimuli. Therefore, what is needed is a behavioral requirement that can be built into the delay of the current DMTS procedure without new stimuli needing to be introduced and that can be applied evenly across all delays.

The second part of Experiment 3.3 took 2 new groups of rats and trained them in a new version of the basic DMTS task used in the current experiments. This new task was essentially the same as the earlier version except that instead of responding in a VI schedule on the back lever during the delay, rats responded on a 4 s differential reinforcement of low response rates schedule (DRL) with a 4 s limited hold. In essence this schedule changes the operant behavior from discrete lever responses to 'wait 4 s, but no longer than 8 s, and then respond'. This task was developed because it more closely resembles the type of delay event that is used with human subjects in either recognition experiments or the Brown-Peterson task. That is, unlike presentation of a reinforcer or light stimulus in the delay, requiring a specific response that differs from what the rat normally performs is more akin to the use made in human research of finger tapping or counting backwards during the delay. However, actual performance at a 0 s delay was not examined. As discussed in Section 1.1.1, the memory task at a 0 s delay is different than the task with a delay because of the use of certain response requirements during the delay. As a result different interpretations can be made of

Brown-Peterson studies, depending on whether 0 s delay performance is included or not. Because the present analysis involves the estimation of 0 s performance from performance following actual delays, a more accurate measure of delay-independent performance can be gained. That is, by using the exponential model of Equation 1 to estimate accuracy at 0 s, actual performance (and the confounds that it introduces) at this delay need not be included in the analysis of performance. This is an important analytic modification over the traditional procedures because of the ability to obtain measures of delay-independent and delay-dependent performance that do not rely on performing in essentially different tasks in order to gain them.

After training in the basic DMTS task, the DRL requirement of the new task was gradually trained. Data was collected prior to and after training in the DRL modified version of DMTS to observe the effect of introducing this requirement on forgetting and delay-independent performance. One group of rats was then given a sham-control lesion, and the other group received a large MS lesion (as per Experiment 3.1, Part 4). The choice of relatively large damage in the MS for the lesioned group was based on the results of the earlier experiments which indicated that disruption to this area may result in performance changes in this task.

Also examined in the final condition of Part 2 was the effect of increasing the exposure of rats to the initial stimulus lever. Previous research has indicated that increasing the exposure to the initial stimulus on a DMTS trial increases accuracy in a delay-independent fashion (e.g. Roberts, 1972; Grant, 1981; see White, 1985 for a review), which is reflected in an increase in *Log do*. Given that Part 3 of Experiment 3.1 indicated that delay events may decrease *Log do* in rats, it was of interest to see whether the potential disruption to performance in the current study would be ameliorated by increasing the initial FR requirement on the stimulus lever, and thus increase exposure to the initial stimulus (as shown by White, 1985 using pigeons). As with all previous DMTS experiments conducted in the present research, the effect of lesions on performance was assessed by measuring performance using *Log d* and then

fitting Equation 1 to describe changes in rate of forgetting and delay-independent performance.

METHOD

Subjects and *Apparatus*

For Part 1 the subjects were the same as those in Experiments 3.1 and 3.2. Rat B1B (a small MS lesion rat) died approximately 3/4 of the way through it's last condition (Condition 1), but enough data was available to perform an accurate analysis. For Part 2, 11 new male rats were trained. These new rats were kept under identical conditions but were 4 months younger than the rats used in Part 1 at the start of Experiment 3.3.

Procedure

Part 1

The basic DMTS task was the same as used in Experiment 3.1 and 3.2. However, there were two experimental conditions which all rats were exposed to, for 32-35 sessions per condition. All rats were trained for 33 sessions of baseline DMTS performance at the beginning of the experiment. Upon completion of the baseline, half the rats in each group received Condition 1 first, and the other half received Condition 2 first. In Condition 1 a free food reinforcer was delivered at the very beginning of the delay, that is immediately after the front lever began to retract. In Condition 2 a free food reinforcer was delivered 3.5 s prior to the completion of the arranged delay for that trial. Therefore, in Condition 1, the third response to the stimulus lever provided access to the reinforcer. For Condition 2, 3.5 s prior to the end of the delay a response on the rear lever produced access to the reinforcer, and this was followed by presentation of the two choice levers (irrespective of the rats behavior following delivery of the delay reinforcer). In three of the chambers, reinforcers were delivered via dippers that when operated provided access to .1 ml of condensed milk for 3.5 s. In four of the chambers, the same volume of condensed milk was delivered via liquid droppers. Irrespective of

the manner of reinforcer delivery rats were very quick to consume them. Sessions were run for 40 mins each.

Part 2

11 male rats kept under identical conditions to those used in the experiments previously described here, served as subjects in Part 2. They were pretrained in the same manner as described in Experiment 3.1. After 60-80 sessions in the basic DMTS task (with no events scheduled during the delay) performance was assessed by using the data from the last 25 sessions. Next, rats were gradually introduced to a DRL requirement in the delay. Every 5th session, the DRL requirement was increased by .5 s, until it was 4 s. The imposition of a DRL requirement in the delay meant that in order for a rat to end the delay, it had to withhold responding for the period of time specified by the DRL schedule. Specifically, responding on a DRL 4 s was shaped up in the delay period such that responses on the rear lever had to be 4 s apart in order to end the delay. Responding within 4 s of the previous response on the rear lever reset the timer and the rat had to withhold lever-pressing a further 4 s before being able to end the delay. A DRL of 4 s was chosen so as to be long enough to require a change in the inter-response time (IRT) distribution by rats, but not so long that delays were unduly lengthened by errors in performing the DRL. Furthermore, previous research has indicated that rats with MS damage perform very poorly with relatively long DRL requirements (e.g. Ellen & Aitkin, 1973). Thus, the DRL requirement had to be of a sufficiently short length to minimise any confounding influence on delays or group differences in ability to perform the DRL requirement.

Because of the difficult nature of the task, performance was shaped slowly and a great deal of training was conducted prior to taking measures of performance. After approximately 40 sessions of introducing the DRL requirement, 30 sessions were conducted at DRL 4 s. Following this, a further 80 sessions were conducted under the same DRL requirement but with the additional requirement of a 4 s limited hold. That is, rats had to respond once between 4 and 8 s after the last response throughout the

delay in order to end the delay. After, this amount of training all rats were performing the DRL requirement well and showing DMTS performance at above chance levels. (Performance in the DRL 4 s condition was assessed at this point by taking data from the last 40 sessions of training). At this point the rats were divided into two groups, with 5 rats receiving a sham-control lesion and the other 6 rats receiving a large MS-lesion. (Surgical procedures were identical to those described in Experiment 3.1). After 3-5 days of recovery, all rats were placed back in the DMTS task with the DRL requirement, and training proceeded for a further 45 sessions (taking the last 40 sessions of data to assess post-lesion performance). Finally, with the DRL still in place, the FR requirement of the present task was altered. Previously, rats were required to make 3 responses on the stimulus lever in order to initiate a delay, for the last 25 sessions of the experiment rats were required to make 10 responses on the stimulus lever.

RESULTS and DISCUSSION

The results of Parts 1 and 2 are presented separately below. In brief, the research showed that presentation of food in the delay (Part 1) and a specific DRL requirement in the delay (Part 2) disrupted DMTS performance. This disruption was manifest in a decrease in *Log do* (delay-independent aspects of performance) under both types of retroactive interference. However, there was no differential effect across different surgical groups.

Part 1

Part 1 examined the effect on performance of altering the location of food delivery in the delay of DMTS trials. The results indicated *Log do* decreased relative to baseline, but *b* was unaltered, with the presence of food in the delay. The effect of *Log do* was more pronounced when the delivery of food was at the end of the delay, but there was no difference between groups in the amount of change exhibited. Using the last 30 sessions in each condition, an analysis of changes in *Log d* as a function of

delay demonstrated that the exponential function (Equation 1) provided a very good summary of DMTS performance irrespective of presence of - or location of a free food reinforcer in the delay for small MS, large MS, MB and sham-lesion groups, as indicated in Figure 3.14 which shows *Log d* plotted as a function of delay for each group and condition in Part 1. Figure 3.15 shows changes in the delay-independent performance measure (*Log do*) and changes in the rate of forgetting measure (*b*) from the plots shown in Figure 3.14.

Figure 3.15 and the subsequent analysis showed that there was no change in *b* as a result of food delivery in the delay, irrespective of whether the delivery was at the beginning or end of the delay. Although Figure 3.15 indicated that there may have been an increase in *b* when food was delivered at the end of the delay for the large MS-lesion group, a one-way repeated measure ANOVA for Condition with Condition as a repeated measure (i.e. no food in the delay present versus food at the beginning of the delay versus food at the end of the delay) for each group separately did not reveal any significant effects ($F<1.0$). Indeed Table 3.4, which gives parameter estimates for individual subjects, shows that only 4 of the 6 subjects in the large MS-lesion group displayed an increase in *b* on trials in which the reinforcer was delivered at the end compared to trials in which the reinforcer was delivered at the beginning of the delay. Figure 3.15 also indicates that the values of *b* (irrespective of delay condition) tended to be largest for the control and large MS-lesion groups compared to the MB and small MS-lesion groups. However, analyses failed to reveal a significant main effect of group on *b* ($F=2.12$).

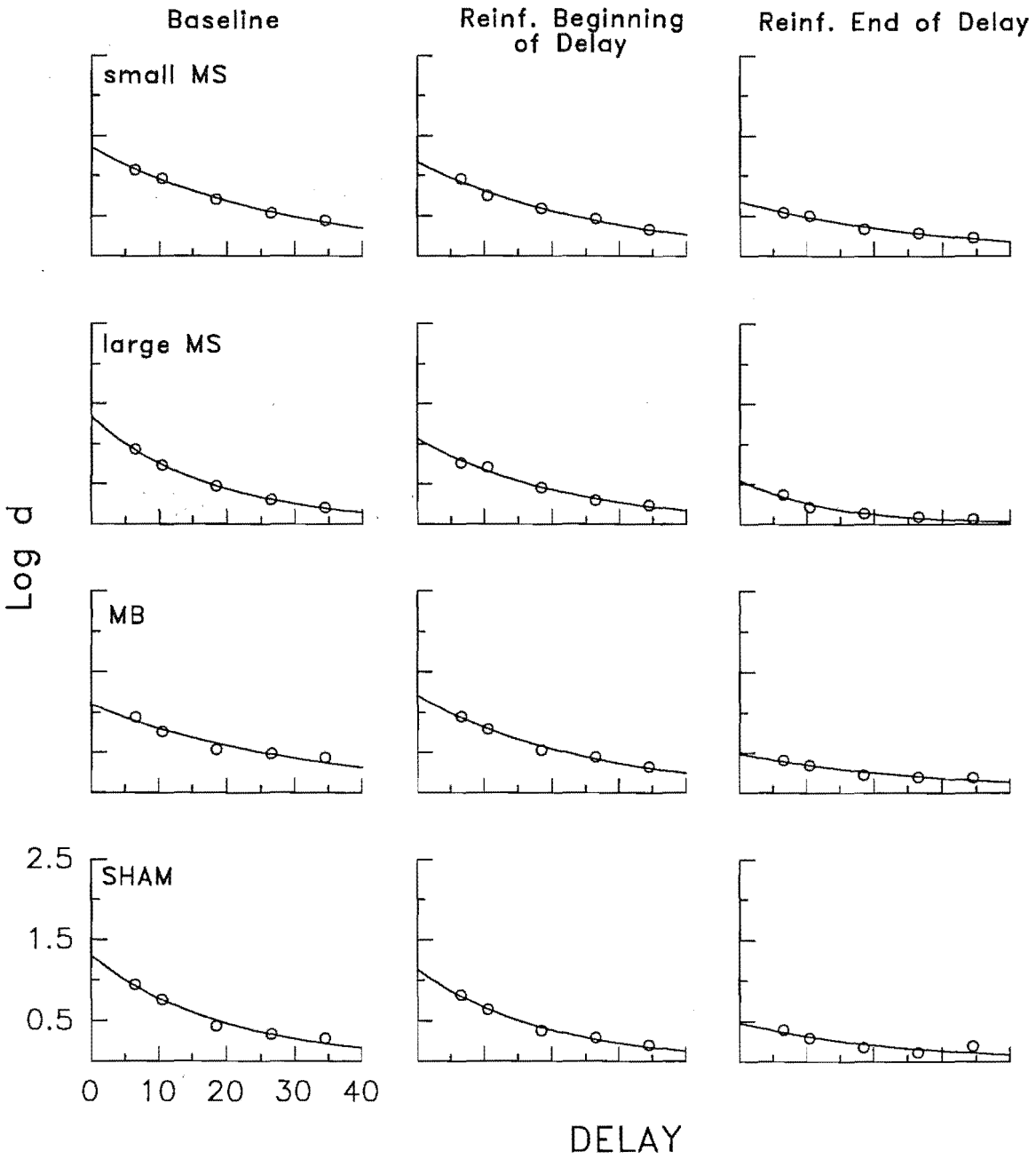

FIG 3.14 Accuracy in the DMTS task (*Log d*) plotted against delay (s) for the small MS (top row), large MS (second row), MB (third row) and sham group (lower row) for performance in the DMTS task with no reinforcer in the delay present (left column), with a reinforcer presented at the beginning of the delay (middle column) and with a reinforcer presented at the end of the delay (right column). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*) - (these are plotted as a function of delay condition in FIG 3.15). The mean squared errors for Equation 1 fitted to the data ranged from 0 to .002.

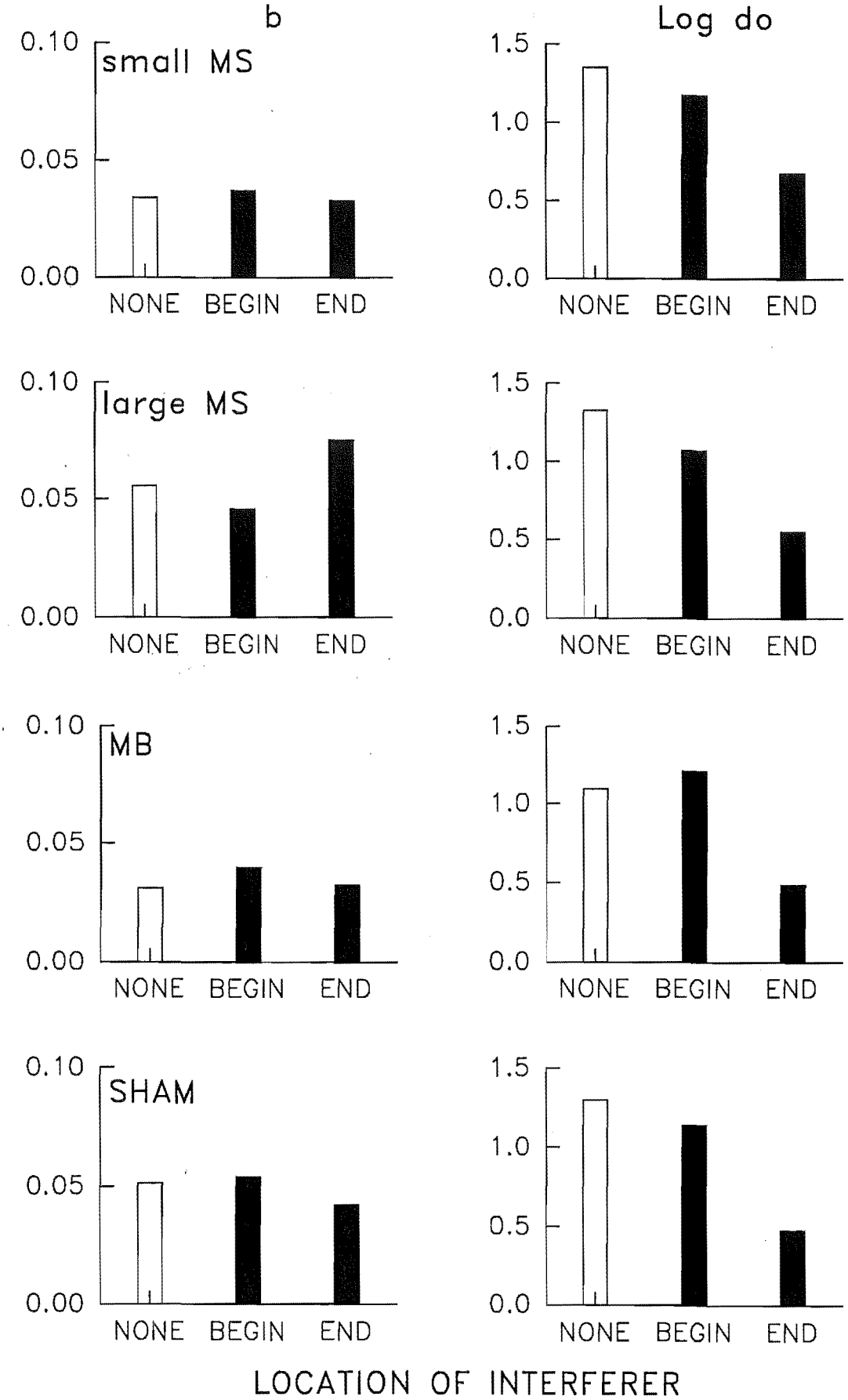

FIG 3.15 Changes in *b* (left column) and *Log do* (right column) as a function of delay condition (baseline - with no reinforcer presented - open bars, reinforcer at the beginning of the delay, and reinforcer at the end of the delay - both in filled bars) for the small MS (top row), large MS (second row), MB (third row) and sham groups (lower row).

The lack of influence that free food delivery at the beginning of the delay had on forgetting in the present experiment confirms the same finding obtained in Experiment 3.1 (Part 3) for the small MS, MB and sham-control groups. However, the present results expanded upon the previous study by demonstrating that alterations in *b* still do not occur if the reinforcer occurs at the end of each delay and that the rate of forgetting is unaltered even in rats with comparatively large MS lesions - a lesion which results in a greater rate of forgetting in the basic task, relative to presurgical performance.

All groups of rats displayed an effect on *Log do* as a result of reinforcers being delivered in the delay. A repeated measure ANOVA of Group x Condition (no free food, food at the beginning of the delay and food at the end of the delay) showed that there was a significant main effect of Condition on *Log do* [$F(2,44)=26.64$, $p<.001$]. Figure 3.15 indicates that delivery of a reinforcer at the beginning of the delay caused a small reduction in *Log do*, relative to when no food was delivered in the delay, for all groups except the MB group. However, this trend was not sufficiently strong to result in a significant difference between *Log do* obtained with no reinforcer present and when a reinforcer was present at the beginning of the delay ($F<1.0$) irrespective of group. When reinforcers were delivered at the end of the delay, *Log do* was significantly reduced relative to when reinforcers were not present [$F(1,22)=36.7$, $p<.001$], and when reinforcers were present only at the beginning of each delay [$F(1,22)=51.7$, $p<.001$]. Furthermore, all subsequent post-hoc comparisons showed that each group showed a significantly lower *Log do* when food was delivered at the end of the delay compared to no food or food at the beginning of the delay (at the $p<.05$ level for the small MS-lesion group and at the $p<.01$ level for the other 3 groups). There was no main effect of Group on the values of *Log do* ($F<1.0$) nor was there an interaction of Condition with Group on the value of *Log do* ($F<1.0$).

Table 3.4 Individual subjects' parameter estimates (*b* and *Log do*) obtained in Experiment 3.3, Part 1. The data is presented separately for each of the three conditions (i.e. no reinforcer in the delay (baseline), reinforcers at the beginning of each delay and reinforcers presented at the end of each delay). *** rat G1B responded exclusively on the left lever when reinforcers were delivered at the end of delay were presented, and thus parameter estimates were undefined and unable to be included in the group data for this condition.

	b			Log do		
	none	reinf begin.	reinf. end	none	reinf. begin	reinf. end
SMALL MS LESION						
B1R	.0328	.0335	.0481	.999	.690	.486
B1B	.0279	.0305	.0249	1.688	1.193	.999
B1G	.0273	.0398	.0358	.945	2.078	1.146
B2R	.0337	.0596	.0431	1.050	.940	.310
B2B	.0294	.041	.0460	1.216	1.098	.955
B2G	.0424	.0589	.0311	1.545	.702	.393
B2W	.0627	.0452	.0726	1.367	.786	.426
E1R	.0293	.0248	.0278	2.091	1.993	1.680
GROUP	.0340	.0371	.0330	1.350	1.173	.675
LARGE MS LESION						
G1R	.0327	.0369	.0828	1.039	1.208	.624
G1B	.0413	.0175	.0***	.858	.713	.0***
G2R	.0716	.0914	.0652	1.558	1.420	.220
G2B	.0454	.0306	.1712	1.217	1.055	1.572
G2G	.0866	.0553	.0644	2.362	1.344	.437
G2W	.0659	.0827	.0288	1.375	1.068	.466
GROUP	.0555	.0459	.0753	1.328	1.069	.550
MB LESION						
D1R	.0344	.0472	.0373	1.343	1.147	.433
D1B	.0454	.0150	.0824	.627	1.318	.363
D1G	.0180	.0450	.0071	.373	.568	.433
D2R	.0586	.0455	.0241	2.136	1.025	.351
D2B	.0111	.0363	.0392	1.860	1.846	1.241
D2G	.0476	.0575	.0543	1.297	1.682	.765
D2W	.0337	.0571	.0514	.412	1.028	.019
GROUP	.0310	.0396	.0324	1.096	1.211	.488
SHAM-CONTROL						
C1R	.0446	.0352	.0324	1.448	1.373	.840
C1G	.0341	.1465	.1060	1.129	2.089	.285
C2R	.0814	.0811	.0707	1.341	.787	.332
C2B	.0688	.0706	.0304	2.134	1.624	.509
C2W	.0287	.0342	.0654	.626	.927	.619
GROUP	.0512	.0540	.0423	1.299	1.141	.480

The influence that free food delivery at the beginning of the delay had on reducing the measure of delay-independent performance in the present experiment confirms the finding obtained in Experiment 3.1 (Part 3) for the small MS, MB and sham-control groups and extends these findings to include the large MS group. The present results also expanded upon the previous study by demonstrating that if the free food occurs at the end of the delay there is an even greater reduction in *Log do*. This differential influence on performance according to the temporal location of delay food was reflected in the observation that reinforcers delivered at the end of the delay reduced *Log do* for all rats except one. Whereas, reinforcers at the beginning of the delay had a different effect across rats, dependent upon their starting baseline level of *Log do*. Specifically,

Table 3.4 shows that amongst the 10 rats that displayed the highest values of *Log do* in baseline, all 10 showed a reduction in *Log do* when reinforcers were presented at the beginning of the delay. However, amongst the 10 rats which displayed the lowest values of *Log do* in baseline, 7 showed an increase in *Log do* when reinforcers were presented at the beginning of the delay. The effect of reinforcers at the beginning of the delay on *Log do* as a product of baseline (no delay food) level was confirmed by a significant interaction revealed by a 2x2 ANOVA comparison of the highest 10 versus the lowest 10 rats (in terms of baseline *Log do* versus reinforcer) by delay condition (no food in delay versus food at beginning of the delay) [$F(1,18)=16.23$, $p<.001$]. (Note that in choosing rats for the 10 'best' by 10 'worst' performers in terms of *Log do*, individuals from all surgical groups contributed to both). Post-hoc comparisons revealed that each group of 10 rats separately displayed a significant alteration in *Log do* ($p<.05$, for the lowest group, and $p<.01$ for the highest group). However, the change in *Log do* was an increase for the lowest group and a decrease in the highest group.

The present results are in contrast with the findings of a number of other studies which have examined retroactive interference effects with pigeon and rat subjects. The strong influence of reinforcer delivery in the delay on *Log do* (particularly when reinforcers were presented late in the delay), but not *b,* in the present experiments was contrary to that observed in pigeons performing a DMTS task with key-light stimuli (Grant & Roberts, 1976; Jans & Catania, 1980; White, 1985), and is contrary to the effect of most delay events on DMTS performance in pigeons (see White, 1985). In addition, the differential influence on performance as a product of when food was presented in the delay was also inconsistent with those previous findings which have shown that the temporal location of houselight illumination in the delay is unimportant in the degree of disruption shown by pigeons in DMTS (Maki et al., 1977). Finally, although the effects of retroactive interference on rats in DMTS has not previously received attention, the highly disruptive effect of a short period of exposure to delay food seen in the present study is in contrast to the lack of disruption seen in some studies following considerable amounts of exposure to food, odours and various visual

and spatial stimuli in 8-arm maze tasks with rat subjects (e.g. Maki et al., 1979; Beatty & Shavalia, 1980; Roberts, 1981). However, other research with rats has shown that performance can be disrupted by delay events (e.g. 3 interpolated runs on extraneous mazes in a delay, Roberts, 1981; and free chocolate delivery in the delay of a SPR trial, Experiment 2.2).

With respect to the unexpected effect of retroactive interference on *Log do* rather than *b*, it may be that the influence observed on *b* in previous studies was because of unequal exposure to the disruptor (whether it be free food or a houselight) across delays. In the present study the same amount of free food was gained at each delay; this had a constant delay-independent effect on accuracy (i.e. a decrease in *Log do*). Whereas in previous studies which have examined DMTS performance over a range of delays, the disruptor was present throughout each delay. Thus, in these previous studies there was greater exposure to a disruptor at longer delays compared to short ones. Such inequalities in the application of interference across delays would be expected to produce the observed increase in *b*. Therefore, the actual effect of retroactive interference may well be delay-independent (i.e. consistent across delays) as observed here, and increases in the rate of forgetting in other cases are the result of increases in the amount of interference as delay length increases. However, while this possibility may account for the lack of *b* change in the present study, it does not account for all the discrepancies between the present and previous results. That is, this explanation does not account for the greater disruptive effect of food at the end of the delay compared to the effect at the beginning of the delay. Nor does this explanation account for the finding that reinforcers at the beginning of the delay have a differential effect on *Log do* dependent upon the baseline level of performance.

The increase in performance in a delay-independent manner for those rats which originally displayed relatively poor performance, and the concurrent decrease in rats which originally displayed good performance, makes interpretation of the effect of reinforcer delivery at the beginning of the delay problematic. One possible explanation

is that although the delivery of free food was designed to be disruptive, the delivery of food in the delay may have inadvertently reinforced the occurrence of various behaviors exhibited by a rat in the delay. It is possible to speculate that behavior within the delay can be divided into two general types: behavior that aids memory performance, and behavior that is irrelevant (and thereby may even be disruptive) to memory performance. Furthermore, it is also possible to speculate that the types of behavior that are helpful to memory occur primarily at the beginning of a trial (e.g. spending time by the lever that was the initial stimulus after being exposed to it, see Part 2 below). Secondly, the types of behavior which may be unhelpful to memory may tend to occur later in the trial (e.g. rear lever bar pressing). Consequently, reinforcers delivered at the end of the delay may be very disruptive to performance (in all rats) because they immediately follow, and hence may 'enhance' or 'strengthen' the occurrence of behavior which tend to be unhelpful to performance (e.g. the rate of rear lever bar pressing may increase). Alternatively, delivery of a reinforcer at the beginning of a delay will have one of two effects, dependent upon the level of performance shown by the rat. Delivery of a reinforcer early in the delay period may tend to follow behaviors (and thereby 'enhance' or 'strengthen' them) which are helpful to performance, but only for rats which do not already engaged in this behavior. Rats that are already performing well, may be expected to be making maximal use of behaviors which may aid performance such as pausing by the stimulus lever. Effectively, the good performers are at a ceiling level of performance and can therefore only be disrupted (albeit minimally) by the delivery of a reinforcer.

If delivery of free food in the delay is acting to adventitiously reinforce various behaviors and thereby disrupt DMTS performance, then a question which arises is, 'how do delay events in the form of extraneous stimulus presentations disrupt performance'? It may be that stimuli presented in the delay disrupt performance because they produce a degrading of salience for the original target stimulus, i.e. stimuli may become confused. Alternatively, similar to the suggested effect of food reinforcers, the presentation of stimuli may result in an increase in behavioral activity in

the delay (presumably behavior of a 'nonhelpful' sort). Thus a critical aspect of whether or not an event in the delay produces memory impairments may be the degree to which a subject engages in behavior irrelevant, or even confounding, to the actual task of remembering a target stimulus. Although the actual determination of the mechanisms by which an event in the delay impairs performance remains a challenge to researchers, Part 2 provided added support for the idea that the behavior engaged in by a subject can be critical in influencing performance in a delay-independent manner without the presence of extraneous stimuli or reinforcers into the delay.

Part 2

Part 2 investigated the potentially retroactive interfering influence of an explicit aspect of a subject's own behavior in the delay on DMTS performance. This study examined the effect of a DRL 4 s, limited hold 4 s response requirement on the rear lever on performance in the DMTS task for two new groups of rats presurgery and following a large MS lesion or sham-lesion surgery.

An analysis of the IRTs displayed by both groups of rats in all phases of Part 2 is given in Figure 3.16. The IRTs for all responses made in each delay by an individual in the last 10 sessions of each condition were placed in 1 s bins. The percentage of IRT s falling in each bin were then expressed as the percentage of all IRT s which occurred, and then each bin's percentage was averaged for the group. Individual rats displayed very little deviation from the group results plotted here. During presurgery baseline (no DRL requirement) both groups displayed IRTs typical of VI responding during the delay period. That is, the distributions were skewed towards short IRT s. Both groups were displaying a very similar pattern of IRT distributions by the end of training in the DRL 4 s, pre-surgery condition. These IRT patterns were maintained without change in both groups throughout the remainder of training following surgery. Thus, the only change in IRTs was the result of imposing a DRL 4 s requirement into the delay. The effect of this DRL was to redistribute responding into roughly a bi-modal distribution. The high proportion of short IRTs was very much decreased, though not entirely removed. The

other modal point was between 4 and 5 s. These results indicate that there was no inadvertent confounding of the effect of the DRL requirement on IRTs from extended training or lesions.

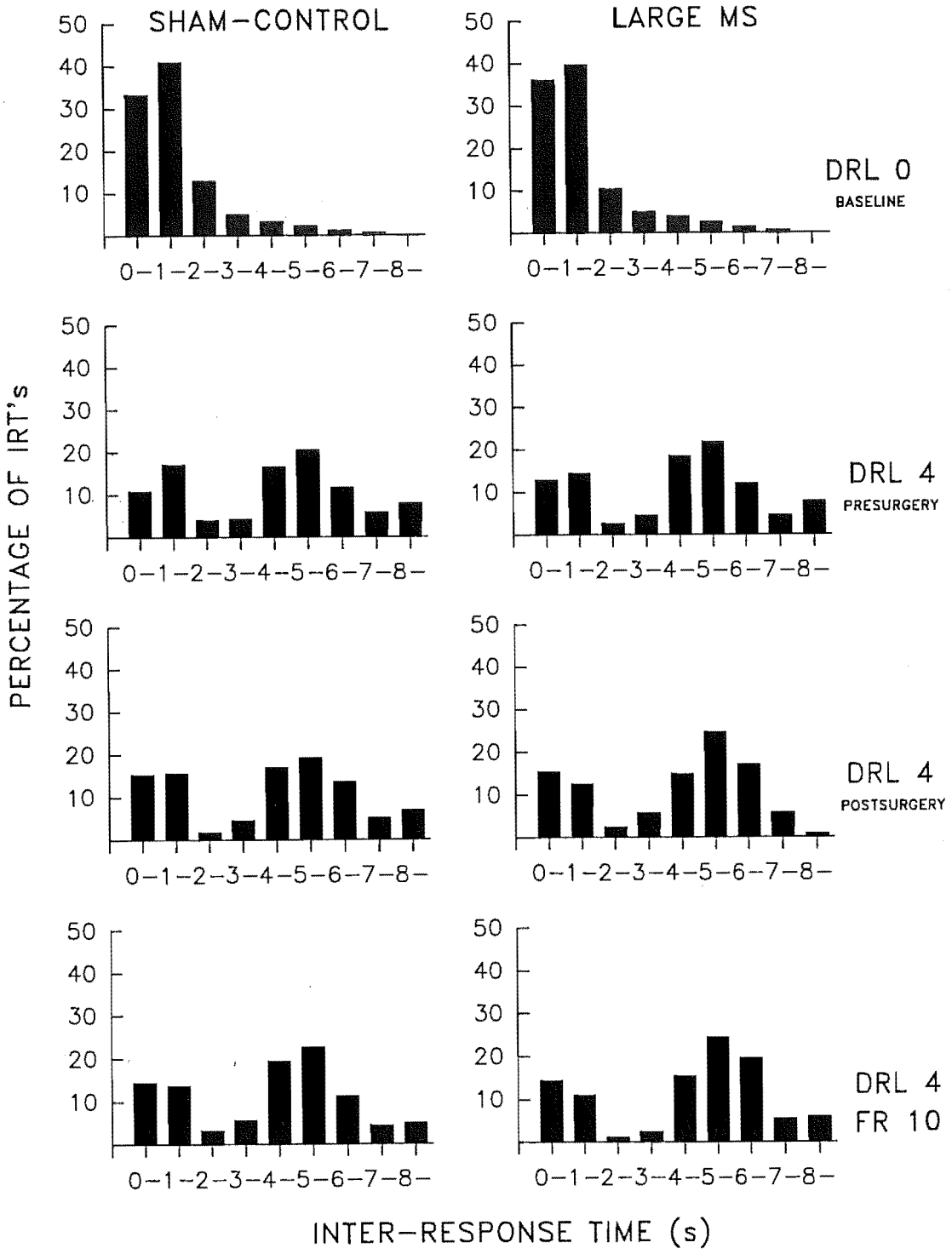

FIG 3.16 Shows the IRTs exhibited by the sham-control (left column) and large MS lesion (right column) groups during the delay period of DMTS trials for each condition in Part 2. The group percentage of IRTs (Y-axis) are shown for successive 1 s bins (x-axis). The group average is a weighted mean of all responses occurring in each bin for all rats in a given group over the last 10 sessions of training in a condition.

An analysis of changes in *Log d* as a function of delay demonstrated that the exponential function (Equation 1) provided a very good summary of DMTS performance in the basic task and when a DRL requirement was superimposed in the delay for both groups of rats examined in Part 2 (large MS and sham-control), as shown in Figure 3.17. Note that the delays are longer (by a constant amount) in all conditions subsequent to DRL 0 s. Delays were measured during Part 2 because of the likelihood of the DRL requirement producing slight increases in them. Indeed, it was found that rats displayed a constant increase of about 3 s in the length of each delay. This increase was virtually identical across subjects presumably as the result of occasional 'errors' in the DRL. Taking the increase in delay into account will tend to raise the value of *Log do* otherwise obtained but will have little or no effect on *b*. Figure 3.18 shows changes in the delay-independent performance measure (*Log do*) and changes in the rate of forgetting measure (*b*) obtained from the data presented in Figure 3.17.

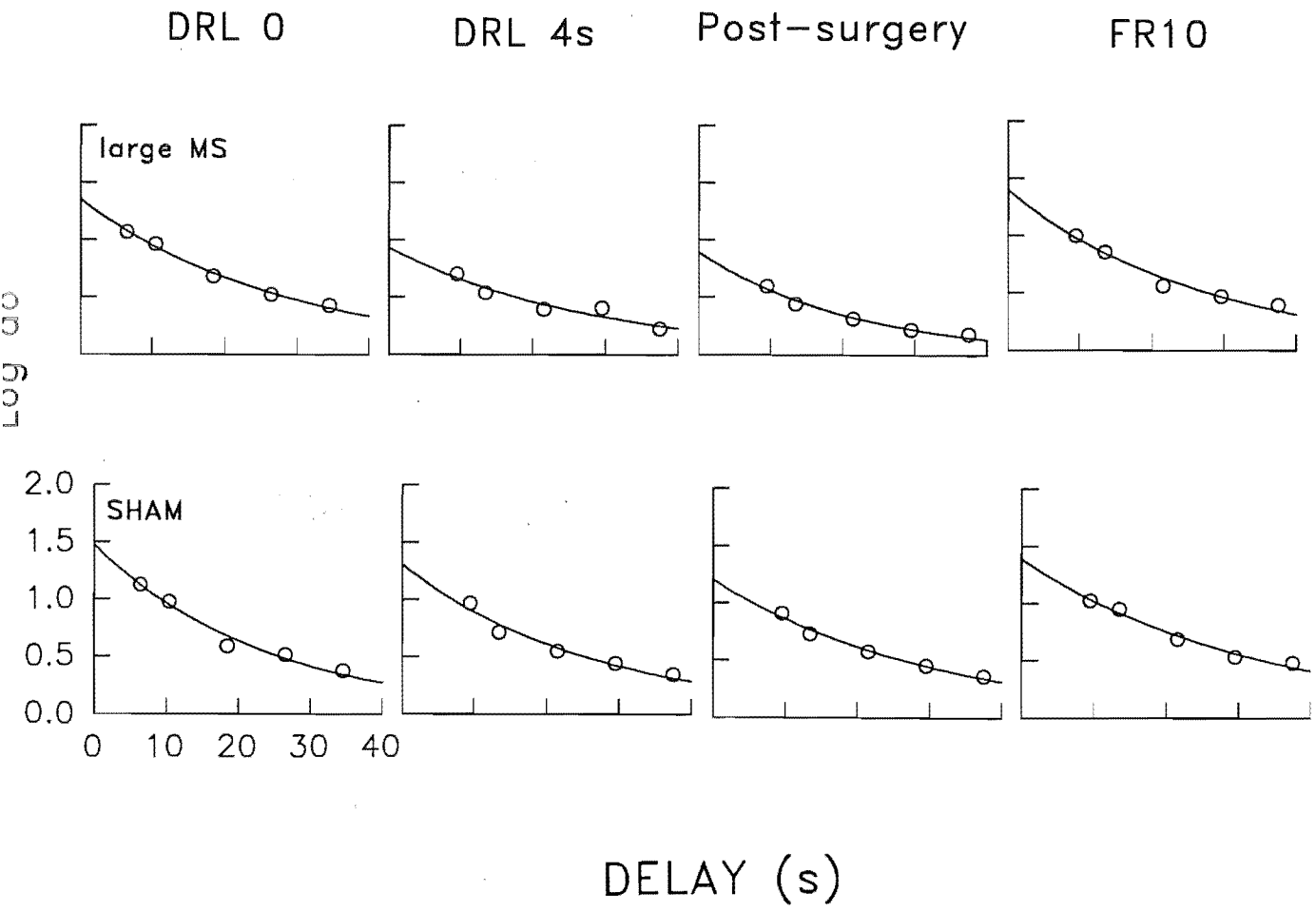

FIG 3.17 Shows accuracy in the DMTS task (*Log d*) plotted against delay (s) for the large MS (top row) and sham-control groups (lower row) for performance in the basic DMTS task with no DRL requirement in the delay (first column), performance in the DMTS task with a DRL 4 s requirement in the delay prior to surgery (second column), performance in the DMTS task with a DRL 4 s requirement following surgery (third column) and subsequent performance when the FR requirement on the initial stimulus lever was increased from 3 response to 10 (final column). Equation 1 was fitted to these plots using nonlinear least-squares regression to provide measures of delay-independent performance (*Log do*) and rate of forgetting (*b*) - (these are plotted as a function of delay condition in FIG 3.18). The mean squared errors for Equation 1 fitted to the data ranged from 0 to .002.

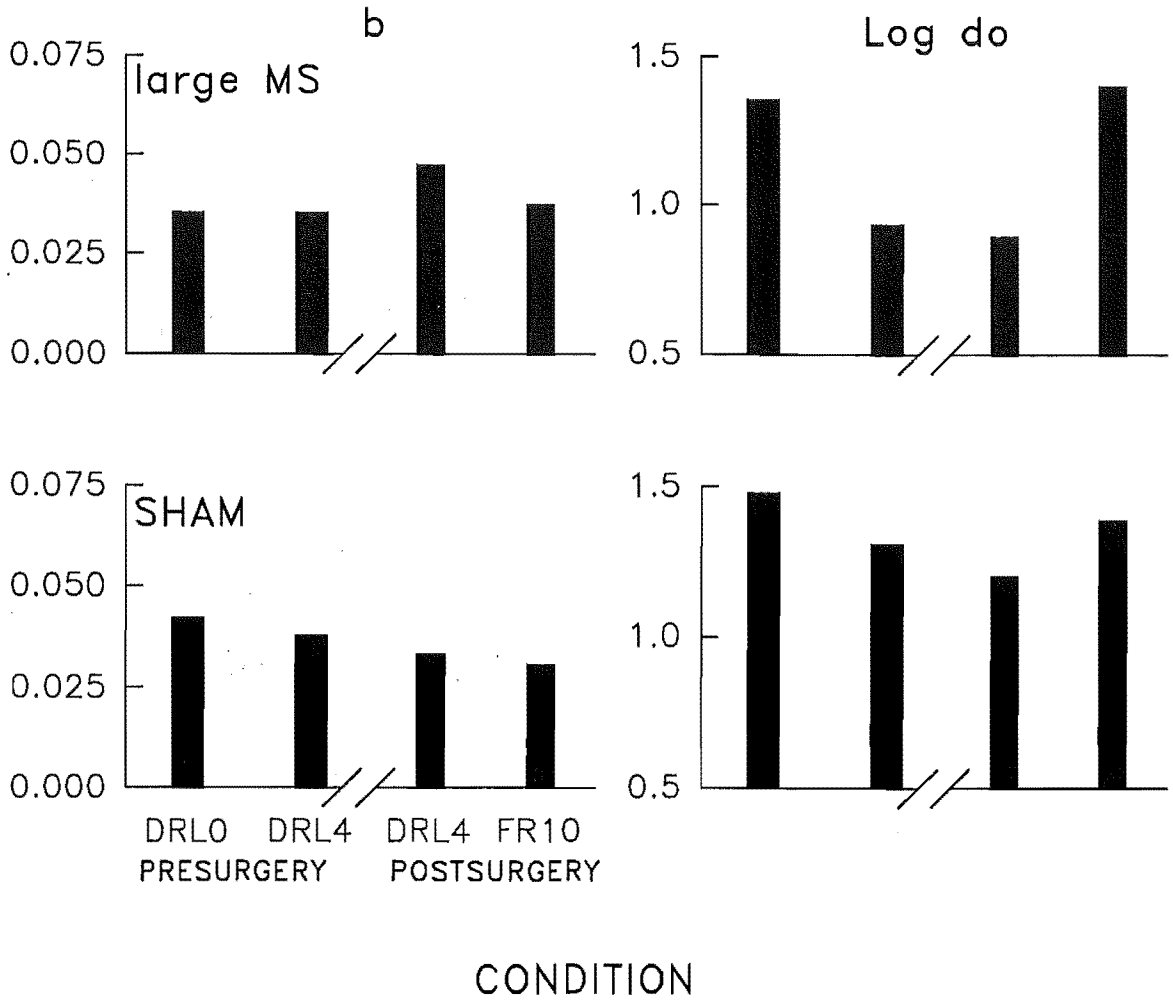

FIG 3.18 Shows changes in *b* (left column) and *Log do* (right column) as a function of condition in Part 2 (baseline - with no DRL requirement, superimposed DRL 4 s requirement prior to surgery, superimposed DRL 4 s requirement following surgery, and following a subsequent increase in the FR requirement to 10 responses on the initial stimulus lever) for the large MS (top row) and sham-control groups (lower row).

Figures 3.17 and 3.18 and subsequent analyses showed that there was no change in *b* as a result of any manipulation to the DMTS task performed in Part 2. That is, requiring rats to perform a specific DRL in the delay did not alter the rate of forgetting in any systematic way. Table 3.5, which presents the parameter estimates for individuals, shows that only 5 out of 11 rats displayed an increase in *b*, in a comparison of performance at DRL 0 and DRL 4 s. Similarly, when the FR requirement on the initial stimulus lever was increased from 3 to 10 responses, there was no change in *b* over all rats or in either group of rats. The lack of alterations in *b* arising from changes in the DRL or FR components of the DMTS task were reflected in the lack of significant effects as revealed by ANOVAs which assessed main effects of Group and Condition, as well as individual assessments for groups separately.

The only significant change in *b* observed in Part 2 was the result of surgery in the large MS-lesion group. Five out of 6 rats in the large MS-lesion group displayed an increase in *b* following surgery, whereas only 1 out of 5 of the sham rats displayed an increase in *b*. The increase in rate of forgetting following MS damage was reflected in the increase for the group *b* in Figure 3.18 and the significant interaction between Group (sham vs large MS lesion) and Condition (pre- vs post-surgery, with condition as a repeated measure) - [$F(1,9)=8.91$, $p<.05$]. This interaction arose because although the sham group on its own failed to show a significant change in *b* ($F=2.52$), the large MS-lesion group did show a significant increase in *b* [$F(1,5)=7.43$, $p<.05$].

In contrast to the effects observed on *b*, *Log do* was unaltered by surgery but substantially affected by alterations in the DRL requirement. Figures 3.17 and 3.18 indicated that delay-independent performance was noticeably reduced by imposition of the DRL 4 s requirement into the delay for most rats (pre-surgery). Indeed, Table 3.5 shows that 8 out of 11 rats displayed substantial reductions in *Log do* across these two conditions. An ANOVA of Group x presurgical Condition (DRL 0s versus DRL 4 s) showed a main effect of Condition on *Log do* [$F(1,9)=5.11$, $p<.05$], but no significant difference between groups or an interaction between Group and Condition ($F<1.0$).

However, Figures 3.17, 3.18, Table 3.5 and an ANOVA of Group x surgical Condition (pre versus post surgery) all indicated that *Log do* was unaltered by surgery for all rats overall and either group individually.

Figures 3.17, 3.18 and Table 3.5 all indicated that the measure of *Log do* was sensitive to an increase in the FR requirement at the start of each trial. That is when the FR requirement was increased, 8 out of 10 rats displayed an increase in *Log do*. A subsequent ANOVA of Group x postsurgical Condition (DRL 4s, FR3 versus DRL 4s, FR 10) showed that the increase in *Log do* was significant with the increase in the FR requirement [$F(1,8)=8.59$, $p<.05$] across all rats, but there was no effect of Group or interaction between Group and Condition. The effect of increasing the FR requirement in the present procedure was the same as observed in previous DMTS studies with pigeons (Roberts, 1972; White, 1985) in that delay-independent performance was increased by increasing the FR requirement on the initial stimulus lever. Effectively, this resulted in a limiting of the disruptive effect that the DRL 4 s requirement had on delay-independent performance, with a similar effect across sham and large-MS lesioned animals.

Table 3.5 Parameter estimates *b* and *Log do* for control and large MS-lesioned rats according to condition in Experiment 3.3, Part 2. Values are given for performance in the DMTS task with no DRL requirement in the delay and a DRL 4 s requirement in the delay pre-surgery; and for performance in the DMTS task with a DRL 4 s requirement post-surgery as well as performance when the FR requirement was increased from 3 responses (as in all previous conditions) to 10 responses. *** F2W died before completion of the FR10 condition, and was therefore not included in the analysis for this condition.

	b				Log do			
	- PRE-SURGERY -		- POST-SURGERY -		----- PRE-SURGERY -----		--- POST-SURGERY ---	
	DRL 0	DRL 4	DRL 4	FR10	DRL 0	DRL 4	DRL 4	FR10
	SHAM-CONTROL							
E1G	.0261	.0395	.0309	.0360	.988	.695	.695	.766
E2R	.0479	.0474	.0366	.0501	1.791	2.218	1.548	2.711
E2B	.0353	.0253	.0214	.0121	1.829	1.468	1.500	1.449
E2G	.0652	.0570	.0555	.0450	1.429	1.354	1.496	1.567
E2W	.0437	.0307	.0347	.0195	1.454	.995	0.952	.823
GROUP	.0421	.0380	.0333	.0306	1.478	1.306	1.203	1.387
	LARGE MS LESION							
F1R	.0308	.0283	.0320	.0178	1.203	.625	1.020	1.858
F1B	.0178	.0426	.0602	.0723	.742	1.015	.578	1.425
F1G	.0205	.0077	.0290	.0220	1.362	.692	.472	.714
F2R	.0442	.0655	.0608	.0508	1.631	1.660	1.115	1.500
F2B	.0528	.0309	.0538	.0582	1.788	1.148	1.501	1.965
F2W	.0526	.0588	.0702	***	1.676	.860	.945	***
GROUP	.0352	.0353	.0473	.0374	1.353	.932	.892	1.399

The effects of retroactive interference observed in Experiment 3.3, Part 2 are largely consistent with the previous findings in Chapter 3. Consistent with Experiment 3.1 (Part 3) and Experiment 3.3 (Part 1), superimposing an event (previously - a reinforcer, presently - a response requirement) had no effect on the rate of forgetting but did result in a delay-independent decrease in accuracy with all groups. Given that the behavioral requirement in Part 2 did not require any new stimuli to be introduced into the delay, the similar disruption to delay-independent aspects of performance across delay events is consistent with the idea proposed in Part 1. Specifically, the disruption to performance arises from an increase or reinforcement of physical activity during the delay. Such activities will tend to be extraneous to the task of remembering and may interfere with performance by restricting the use or effectiveness of helpful behaviors which would otherwise be able to aid memory (e.g. pausing by the initial stimulus lever). Therefore, requiring rats to perform activities which should be helpful (e.g. longer exposure to the initial stimulus by increasing the FR requirement) should counteract the effects of increased activity on unhelpful behaviors during the delay - indeed this was observed in the last condition of Part 2.

Despite the possibility that increased activity in the delay may account for the disruptive effects of various delay events on DMTS performance in Chapter 3, why this disruption is reflected in terms of a delay-independent alteration remains unclear. In Part 1 it was suggested that the delay-dependent alterations in performance seen in a number of other studies was the result of greater exposure to disruption for longer delays relative to shorter ones. Thus, when a constant amount of disruptor was applied across delays a delay-dependent change might be expected; the effects of a constant amount of food access within delays in Part 1 were consistent with this. However, in Part 2 the application of disruption was not constant across delays because rats had to perform on the DRL 4 s schedule throughout the entire delay irrespective of delay length. Therefore the effect of DRL requirement, according to the logic given above, should have been greater at longer delays compared to shorter ones and thus resulted in an increase in the observed rate of forgetting - this did not happen. Therefore, it

remains unclear why some procedures have shown an increase in the rate of forgetting whereas those used here consistently show a delay-dependent alteration in performance in the presence of retroactive interference.

The effects of large MS lesions in the current experiment were consistent with the previous research in Chapter 3. As observed in Experiment 3.1 (Part 4), a relatively large amount of damage to the MS had no effect on delay-independent performance but did result in an increase in the rate of forgetting. This increase in *b* observed with the large MS group as a result of surgery was not because of an increased sensitivity to pre-existing retroactive interference in the DMTS task (e.g. responding, albeit 'freely', on the rear lever in the delay). That is, arranging for relatively greater retroactive interference (superimposing reinforcers or response requirements into the delay) did not increase *b* further for the large-MS lesion group. Furthermore, when delay events acted to disrupt performance, they did so in a delay-independent manner (i.e. a decrease in *Log do*). Throughout Chapter 3 the effects of delay events on *Log do* were the same across groups. Therefore, neither MB nor MS-damaged (large or small) rats were shown to be more susceptible to retroactive interference than control rats. Thus, it seems unlikely that exposure to events (e.g. arm stimuli, reinforcers at the end of sample arms, or simply running down subsequent list arms) following initial stimulus presentation was responsible for the severe disruptions observed to memory for early list items observed for small-MS lesioned rats in the SPR task of Experiment 2.3. In conclusion, although large MS damage can cause an increase in the rate of forgetting and small MS damage is sufficient to produce impaired primacy, these alterations in performance are not due to a heightened susceptibility to retroactive interference. The implications arising from the observed lack of interaction between lesion type (or size) and the disruptive influence of retroactive interference are discussed in greater detail in Chapter 4.

Chapter 4 GENERAL DISCUSSION

Recap of the Major Issues Addressed in the Present Research

The present set of experiments investigated the effects of damage to two brain regions connected to the HF (the MS and MB) on memory performance in rats. Implicit throughout the research was the assumption that the study of memory performance under conditions in which the functioning of these two regions is disrupted will provide clues as to their roles in normal memory processes. The two main issues addressed in this research can be summarised as: 1) what are comparative effects of MS and MB lesions on memory performance in the SPR and DMTS tasks, and 2) how do these effects compare with other lines of evidence implicating these two regions in memory. The conclusion from a review of the relevant literature in Chapter 1 was that the MS (via its cholinergic input to the HF) is a critical brain region with respect to memory function. Evidence supporting this conclusion came indirectly from human clinical data with AD and KS subjects, both of which show a variety of similar memory impairments and display neuropathology in the MS region (amongst other regions). Also, human and nonhuman pharmacological experiments in which levels of CNS acetylcholine were manipulated have shown that the reduction in cholinergic activity results in many memory impairments which are similar to those observed in AD and KS. Finally, more direct evidence comes from studies which have shown that experimentally-induced lesions of the MS area reliably produce a variety of memory impairments in rats and that the greater the damage caused, the greater the loss of cholinergic activity in the HF, and the greater is the resulting memory impairment. Likewise, there are also several lines of evidence supporting the conclusion that the MB brain region plays an important role in memory function. For example, KS subjects also display neuropathology in the MB region and although there is some debate about the reliability of the effect, a number of nonhuman studies have shown that lesions in this area produce memory deficits. Therefore, both the MS and MB brain regions are implicated in memory via similar lines of evidence and are thus both interesting sites of investigation in the attempt to explore the neurological bases of memory.

In addition to be being interesting in their own right, the MS and MB regions serve as interesting comparisons to one another. Although they are anatomically connected to one another and with the HF, of the two only the MS provides a major cholinergic input to the HF. Thus, lesions of the MS may result in a pattern of memory deficit consistent with that seen in AD, KS, and the human and nonhuman pharmacological data, if indeed this region's role in memory is via its cholinergic input to the HF. Whilst also implicated in memory function, the MB are not a site of neuropathology common to both disorders (although they are implicated in KS) and this region does not contribute to the cholinergic input of the HF. Therefore although both regions may be involved in memory, their neurological mechanisms of action appear to differ and consequently the extent or pattern of deficit which occurs following damage to each may also differ. The respective roles played in memory of the MS and MB regions were a major focus of the present studies.

While a number of studies have investigated MS and MB lesions using a variety of procedures, few studies have simultaneously compared these two regions in a single procedure. A more systematic comparison of these two regions is highly desirable if we are to determine the degree to which either is involved in memory function. In addition, the comparison of MS and MB lesion effects with the various existing lines of evidence may yield a more comprehensive analysis of their respective functions. For example, the examination of MS and MB lesion effects will have implications not only for understanding normal memory function but also the neurological bases of the memory impairments in AD and KS. In this respect, the increasing use being made of analogous tasks with humans and non-humans is a desirable development if we are also to make use of these traditionally separate lines of research in drawing any conclusions.

The same literature which has suggested that the MS and MB regions are involved in memory function also indicated that certain types of task were likely to be useful in exploring memory performance, two of these (the SPR and DMTS tasks) were used

here to address the issues raised above. The animal literature has shown that a maze-based SPR task could be effectively used to explore memory for list items and that the SPE observed with this task is sensitive to lesion effects in rats. Furthermore, there was existing evidence that at least with respect to MS damage there may be impairments in memory for list items similar to those observed in AD and KS. However, prior to the current research the effects of MB damage on memory for list items was unknown. Also, there was some doubt about whether a clear SPE, analogous to that observed with humans, could be shown in rats. The research conducted in Chapter 2 therefore addressed three issues: 1) the establishment of a clear and robust SPE in rats using a 12-arm maze SPR task, 2) the similarity of the resulting SPE to that observed in other species, and 3) the comparative effects of MS and MB lesions on the SPE. The expectations were: 1) that the 12-arm maze version of the SPR used here would result in a clearer demonstration of both primacy and recency effects than seen in previous research, 2) that manipulations which indicate that the primacy and recency effects are independent of one another in human subjects would also differentially effect the primacy and recency effects in rats, and 3) that MS lesions and MB lesions would both disrupt the SPE, but that the MS lesion would be the one most likely to produce a deficit that was similar to the deficits observed in AD, KS and under pharmacological disruption to CNS acetylcholine.

With respect to the use of a DMTS task, the human clinical data had indicated that a distinction between rate of forgetting and delay-independent performance may be a useful distinction to make in the assessment of memory performance. Although the human literature has not yet provided a definite answer as to which aspect of performance may best characterise the memory impairments in AD or KS. In addition there is a substantial amount of existing nonhuman research (mainly with pigeons) which has explored these separable aspects of DMTS performance and subsequently proposed ways to quantify them. However the DMTS itself, and particularly the proposed analyses, have only recently come to be applied to questions of brain region function and thus relatively little is known about the effects of damage on delay-

dependent versus delay-independent performance. For instance, although the effects of MB damage on DMTS and DNMTS performance has been explored, the results are equivocal and the effect of MS lesions on performance in these tasks is largely unknown. Although indirect evidence from the effects of fimbria-fornix lesions and pharmacological disruption to CNS acetylcholine suggests that MS damage may indeed impair DMTS performance, these two sources of evidence differ in terms of the nature of the memory disruption observed. Thus, Chapter 3 explored the effects of MS and MB lesions on DMTS performance using a quantitative model suggested by White and McKenzie (1982) to assess the delay-independent and delay-dependent (rate of forgetting) changes in performance pre- versus post-surgery and compared to a sham-control group. The expectation from Experiment 2.3 was that the MS rather than the MB region was likely to result in impaired performance, but previous evidence indicated that both lesions may result in impaired memory. Thus, a major question was whether either lesion resulted in deficits that were best characterised primarily as a delay-dependent or solely as a delay-independent change.

A major contribution of the present research was the exploration of which aspects of a memory task are critical in determining the extent and nature of a performance deficit following brain damage. This is an issue seldom addressed by previous lesion research, yet there are indications from the human clinical data in particular that such an investigation may be very informative in revealing differences between subject groups that are not always obvious from performance on the basic task. For example, various proactive and retroactive sources of interference influence performance during any memory task. It may be that pronounced performance deficits arise because of heightened susceptibility to these forms of influence. Thus the examination of the interactive effects of brain damage with various sources of proactive interference (stimuli and responses on previous trials) and retroactive interference (food delivery and specific behavioral requirements during the delay period) was conducted in order to further define the manner in which MS and/or MB damage influences memory function. Therefore, the current experiments (mainly in Chapter 3) addressed the

following major questions: Firstly, is there an observable influence of either proactive or retroactive interference on the performance of rats in any group; second, is the effect of interference different for the different groups; and third, to what extent can lesion effects on basic task performance be accounted for in terms of a susceptibility to interference?

The results and implications of the current research are discussed below. In the first instance the basic lesion effects in SPR and DMTS tasks will be dealt with, followed by a discussion of the interaction between these lesion effects and various sources of interference. However, since much of the discussion of lesion effects relies upon conclusions drawn from the DMTS studies, it is necessary to briefly cover some of the concerns and assumptions related to the use of the exponential model to assess performance in this task.

The use of the Exponential Model to Study Memory Function

The advantage of the present approach, employing an appropriate quantitative model, was the separation of delay-dependent and delay-independent aspects of behavior, both of which influence overall performance. That is, the use of the exponential decay function, used primarily in the present DMTS studies, allowed for the assessment of mnemonic decay and its separation from other aspects of performance. Although the exponential model was of great utility in this context, there exist other functions which may also provide a good description of behavior (e.g. hyperbolic function). For the present purposes the choice of descriptive model was not critical. However, in order to be confident about many of the conclusions regarding the effects of MS lesions, several concerns need to be addressed.

An integral component of the present approach was the measurement of accuracy using the bias-free measure *Log d*; which the exponential function was fitted to in order to derive *b* and *Log do*. However, the use of *Log d* is not without its potential problems. As outlined in Section 1.3.2, *Log d* is derived from a consideration of the generalised

matching law (Baum, 1974). Davison & Tustin (1978) proposed the following two equations to describe performance on trials when stimulus S1 was presented:

$$\log (C1/E1) = ar1 \log (R1/R2) + \log c + \log d$$

and when S2 was presented:

$$\log (E2/C2) = ar2 \log (R1/R2) + \log c - \log d$$

where *Log d*, C and E are the same as outlined in Section1.3.2, and *log c* is a constant inherent bias. The obtained reinforcer ratio *Log (R1/R2)* quantifies a reinforcer bias and the parameters *ar1* and *ar2* measure the sensitivity of the response ratios to changes in reinforcement (McCarthy & Davison, 1981). Given these two equations the measure of *Log d*, independent of reinforcer and inherent bias, can be calculated by subtracting the second equation from the first and assuming that R1=R2 (or if not then *ar1=ar2*). Therefore, *Log d* will not be free of reinforcer bias if the number of reinforcers gained is unequal across stimuli and the sensitivities *ar1* and *ar2* are unequal. As noted earlier, the confounding influence of bias may produce spurious changes in the *b* and *Log do* parameters.

The danger of unequal reinforcer rates across alternatives can be overcome by the use of controlled reinforcer procedures (Harnett, McCarthy & Davison, 1984). Thus, an attempt was made at the beginning of the current DMTS research to control reinforcer ratios by restricting the availability of reinforcers to one alternative until a correct response had been made on the other. However, under such an arrangement it was found that responding was extinguished altogether despite extensive attempts to maintain responding. Given the inability to introduce a controlled reinforcer procedure and thus maintain the reinforcer ratio at 1, the validity of the current calculations of *Log d* were dependent on assuming that sensitivity to the reinforcer ratio was equal across alternatives and delays. Whilst such an assumption was made in the present research,

its validity could only be addressed by varying the reinforcer ratio at each delay in each condition, and thus we were restricted to point estimates of discriminability (as indeed has been the case with the vast majority of studies in this area). Notwithstanding the need to rely on these assumptions, the measurement of accuracy using *Log d* and the exponential model of memory performance, which utilises these measures, served as a valuable analytic tools in the exploration of lesion effects in the present research.

With respect to the exponential decay model itself, in order to be confident about changes in delay-dependent as opposed to delay-independent changes, the two parameters (*b* and *Log do*) need to be shown to be empirically independent and the function must fit the data well. Because the parameters obtained from the function describe theoretically separable aspects of behavior, the parameters themselves should be independent of one another, i.e. changes in one parameter should not always be accompanied by changes in the other. The independence of *b* and *Log do* was demonstrated by the discrepant effects of surgery and behavioral manipulations on changes in these parameters. For instance, while large MS lesion surgery altered *b* without changing *Log do*, the placement of events in the delay reliably altered *Log do* without changing *b*. Thus, changes in *Log do* were not necessarily accompanied by changes in *b*, and vice versa. Such independence of these parameters is consistent with previous observations (e.g. Kirk et al., 1988; White, 1985). Erroneous conclusions about parameter changes may also potentially arise from poor fits of the model to the data. For instance, the increase in *b* following large MS damage may be a spurious result of higher variance in measures of *Log d* across delays in this group following surgery. Both variance accounted for and mean squared error measures indicated that the exponential model fitted the data very well, irrespective of group and manipulations of interference.

A final concern regarding the use of the exponential model to describe performance is the question of whether changes in *Log do* or *b* arose due to changes in response bias, or as a product of changes in recognition. The present approach treated

response bias as a potential confounding influence on those aspects of performance assumed to be involved in actual memory function. As discussed in Chapter 1, the *Log d* measure of accuracy proposed by Davison & Tustin (1978) eliminates the influence of a continuous tendency (throughout a condition) to favour one response over another. Hence, the observed changes in *Log do* and *b* in the current DMTS studies were not the product of variations in such biases across delays. However, other forms of bias, unaccounted for by the present analysis, may have potentially influenced the values of *Log do* and *b*. Specifically, subjects may adopt a strategy of switching the side they 'prefer' every few trials or even every few sessions. Indeed, on several occasions such switching appeared to occur, although it was never a regular or systematic feature of responding. Under this sort of response bias, estimates of *Log d* would decrease due to a failure to account for the strategy adopted, and thus perhaps reducing the value of *Log do*. However, there is no reason to suspect that such response biases exerted a significant influence on the calculation of *Log d* or occurred unequally across delays and thus exhibited an influential effect on decay rate. Thus, given that spurious parameter changes were unlikely to be a feature of the present analyses it is possible to be confident about the changes (or non-changes) themselves and hence the results which formed the basis of the conclusions drawn throughout the following discussion.

Basic Lesion Effects on Memory Performance

As the overview of Chapters 2 and 3 below will show, the present research demonstrated that performance on both the SPR and DMTS tasks was impaired following MS damage, whereas for rats with MB damage performance was only mildly disrupted in the SPR task. The impairments following MS damage were best characterised as: 1. both a general reduction in accuracy as well as a total removal of the primacy effect in SPR, and 2. as an increase in the rate of forgetting in DMTS.

Chapter 2 presented a series of SPR studies which first sought to establish the existence of a robust SPE in rats, as well as investigate the effect of delay and interference on memory for list items. These issues were addressed in Experiments

2.1 and 2.2. Experiment 2.1 showed that the current 12-arm maze version of the SPR task resulted in a clear and robust SPE with both primacy and recency effects present. The present task was thus a valuable extension of previous studies which have explored lesion effects on memory for list items in that the behavioral phenomena in question was more clearly demonstrated than in earlier research. Experiment 2.2 showed that the resulting SPE was in many ways analogous to that seen in humans, thereby supporting the conclusion that similar memory phenomena can be studied across species. Therefore, the examination of the effects of brain damage on memory for list items may be usefully compared and integrated across different species.

Given that the SPE found in rats appeared to be similar to that obtained with analogous tasks used with human subjects and sensitive to similar manipulations, the effects of MS and MB damage on this task were examined in Experiment 2.3. Consistent with expectations, this study provided further evidence that the MS region of the rat brain plays a role in memory function, as revealed by the disruptive effects of this lesion on memory for list items. In addition, MB damage was also shown to impair SPR performance. However, the pattern of disruption was different across lesion groups. The MS lesion resulted in a greater reduction in overall accuracy compared to the MB lesion. Furthermore, the MS lesion resulted in a distinctive removal of the primacy effect with a retention of a recency effect. Whereas, the MB lesion removed both the primacy and recency effects. As will be discussed below, the effects of MS damage in Experiment 2.3 were largely consistent with those observed in AD, KS and under the influence of pharmacological disruption to CNS cholinergic activity.

The studies in Chapter 3 investigated the effect of MS and MB lesions on performance in an operant DMTS procedure. The results of Experiment 3.1 showed that MS and MB lesions comparable to those given in the SPR study did not result in any alteration of DMTS performance, pre- versus post-surgery or compared to a sham-control group. However, a slightly larger MS lesion (still restricted to the MS region) did result in an increase in the rate of forgetting with no general delay-independent

suppression in performance across all delays. This basic effect of a relatively large MS lesion on rate of forgetting was subsequently demonstrated again in Part 2 of Experiment 3.3 using a different group of rats trained under a slightly different procedure. The greater rate of forgetting shown by MS-lesioned rats provides for an interesting comparison with other lines of evidence suggesting that this structure plays a role in memory that may be best characterised in terms of the delay-dependent aspects of performance. For instance, as will be discussed below, the observed increase in rate of forgetting is consistent with the effects of fimbria-fornix lesions (which separate many structures including the MS from the HF) as well being consistent with some (but by no means all) of the previous memory research with AD and KS subjects.

Taken together the results of the basic lesion effects on SPR and DMTS performance provide strong evidence for the conclusion that the MS appears to be more critically involved in both memory tasks than the MB. Extensive damage to the MB failed to result in the significant disruptions to memory observed following MS damage. Indeed, the only disruptions observed in performance following MB damage throughout the SPR and DMTS research was the slight disruption of the SPE in Experiment 2.3. The lack of consistent effect due to MB damage appears inconsistent with the observation of a delay-dependent impairment in delayed alternation (Tako et al., 1988) or a delay-independent impairment observed by Saravis et al. (1990) in an 8-arm maze DNMTS task, as well as the finding of MB damage in KS subjects who show a variety of memory impairments (Mayes et al., 1988). However, the present lack of evidence for a role of the MB is consistent with a number of studies which have failed to observe an impairment following MB damage, for example in a Y-maze DNMTS task (Aggleton et al., 1990) and in an automated DMTS task very similar to that used here (Aggleton et al., 1991). Consequently, there appears to be only limited support for a critical role of the MB region in memory and it remains unclear under which conditions or in what manner a deficit may be exhibited following damage to this structure.

Before leaving the MB lesion findings and discussing the MS lesion findings, it should be pointed out that the MB lesions described in Chapters 2 and 3 did not extend to include the supra mammillary region in many of the subjects and in no subject was this region entirely removed (see histological results in Appendix A). As a result many of the current conclusions regarding the effects of MB lesions are perhaps best restricted to only one of the two major mammillary regions projecting to the HF, namely the medial mammillary area. Unfortunately, there were not enough subjects in the MB groups to compare the effects of damage restricted to the medial as opposed to both medial and supra mammillary areas, and future research may profit by doing so. However, in respect to the current research, the medial mammillary region was the most interesting of the two regions because of the neuropathological findings of both Mair et al. (1979) and Mayes et al. (1988) who have reported that this area is severely damaged in KS (although neither study specifically mentioned the supra mammillary region).

Consistent with the expectations based on a review of the existing lines of evidence, MS damage was found to impair memory performance in both SPR and DMTS procedures. Despite a number of problems in comparing these two procedures, since they differ in a number of respects (e.g. type of stimulus, number of trials, length of delays and ITIs), the findings of the current SPR (with the small MS group) and DMTS (with the large MS group) studies were largely consistent with one another in that accuracy was significantly reduced in both following MS damage. Furthermore, the DMTS results were consistent with the possibility that the reduction in the primacy effect was also due to an increase in the rate of forgetting following presentation of a list arm. That is, the primacy effect may have been more severely reduced than the recency effect due the longer period of time between presentation of items at this list position, compared to later list items, and recognition.

Unfortunately, confirmation of this potential cause of the reduction in primacy following MS damage was hindered by a 'Catch 22' situation. The rate of forgetting at

different serial positions can be assessed (as was done in Experiment 2.2) by imposing a range of delays between completion of list presentation and recognition. However, even at a relatively very short delay (10 s), the MS lesion resulted in a total removal of the primacy effect, therefore longer delays post-lesion would be uninformative regarding the rate of forgetting. The delay between early list item presentation and subsequent recognition could have been reduced (and thereby potentially reduce the severe impairment to primacy) by presenting a shorter list, but as argued in Experiment 2.1, a shorter list may not result in a maintenance of clear primacy and recency effects. Furthermore, as shown in Experiment 2.2, the presence of a delay between list presentation and recognition has an unequal influence on the rate of forgetting at the primacy and recency ends of the SPE. Nevertheless, the fact remains that 'primacy' items normally enjoy an advantage over other list items in terms of decay rate (shown in Experiment 2.2), and the MS lesion seems to have eliminated the source of that advantage. An interesting implication of these results is that the primacy effect is not the result of enhanced attentional processing for early list items (as has sometimes been claimed, e.g. Gaffan, 1983) because such an attentional advantage would be reflected in terms of a delay-independent measure of accuracy (*Log do*). Contrary to this interpretation of primacy, the curve fits in Experiment 2.2 showed that the difference between primacy and recency effects was in terms of rate of decay (*b*), and in addition the removal of the primacy effect, via MS damage, appears to be the result of an increase in the rate of forgetting.

Lesion Effects, Memory and Interference

A major focus of the present research was an examination of the interaction between lesion type and various sources of interference. The effects of events which occur prior to the current trial and during the delay period of the current trial (respectively referred to as proactive and retroactive sources of interference) were assessed mainly in the context of the DMTS procedure. The automated DMTS procedure affords a great deal of control over these various aspects of a memory task and has been successful in examining intact animal memory performance (e.g. White,

1985; Edhouse & White, 1988; Jans & Catania, 1980; Dunnett et al., 1990). However, the interaction between the effects of lesions and the effects of such interference had not been a focus of previous studies.

In the examination of interference effects, three major questions were at issue: First, can the influence of proactive or retroactive interference could be demonstrated in rats, irrespective of group? This is an important question in that much of previous nonhuman operant DMTS research has been conducted using pigeons and, in comparison, very little is known about rat DMTS performance. Indeed, several authors have indicated that some types of memory task with rats are highly resistant to the presence of potential disruptors (e.g. Maki et al., 1979; Roberts, 1981). The second question was if there is an observable effect of interference, whether this has a differential influence across experimental groups? This question is of importance because the human data has indicated that a feature of both AD and KS subjects is a susceptibility to the disruptive effects of proactive and retroactive interference (e.g. the Brown-Peterson and prior list learning effects discussed in Section 1.1.1). Thirdly, if there is an interaction between lesion type and the influence of interference, to what extent can the lesion effects on basic task performance be accounted for in terms of a susceptibility to this interference? For example, memory deficits in basic SPR or DMTS performance may have emerged following MS damage because of increased susceptibility to the influence of events which occur during the delay (e.g. rear lever responding to centre the subject) and/or from previous trials (e.g. the stimulus or response on the immediately preceding trial) in this group. Closely related to this third issue, the investigation of proactive and retroactive interference effects was necessary in order to explore which aspects of the memory-task may have contributed to the differential sensitivity of the SPR and DMTS tasks in revealing lesion effects. These issues are discussed separately below for retroactive and proactive interference.

Interference Effects on Memory

With respect to retroactive interference, both the SPR and DMTS procedures were effective in showing that events placed during the delay period could be extremely effective in reducing accuracy. Experiment 2.2 showed that free food access during the delay removed the recency effect while primacy was unaltered. Further, Experiment 3.3 showed that free food was extremely effective in producing a general, delay-independent, reduction in performance especially if it occurred late in the delay period. Similarly, requiring a specific DRL response requirement in the delay in a manner more akin to the type of procedure used with humans was shown to be effective in producing a significant delay-independent reduction in accuracy. Although there are no relevant DMTS studies with rats with which to compare the present findings, both the DMTS and SPR results strongly argue against the general conclusions from maze-based studies (e.g. Maki et al., 1979; Roberts, 1981) that rats are largely insensitive to the disruptive effects of retroactive interference. The implication of these present findings is that the observation of, or severity of, retroactive disruption is dependent upon on the type of disruptor and probably the specific nature of the task. However, the conditions under which retroactive interference effects can be observed in rats currently remain unclear. For example, a clear reduction in accuracy for most rats following free food in the delay period of the DMTS trials only occurred when food was delivered at the very end of the delay. Possible reasons for this finding (to do with the behavior engaged in during the delay) are suggested in the Discussion of Experiment 3.3, and this issue will require further investigation.

With respect to proactive interference, the manipulations of ITI in combination with a more molecular analysis of DMTS performance provided a very convincing demonstration of the influence that such interference can exert on performance. The present research showed that events prior to the current trial had an impact on both delay-dependent and delay-independent aspects of performance. As far as such a comparison was possible, the present results were similar to previous findings with rats on this task (Dunnett & Martell, 1990). Although, the exact patterns of influence

observed in rats arising from previous trial stimuli and responses were not found to precisely mirror those seen with pigeons (Edhouse & White, 1988 - see Discussion in Experiment 3.2).

In summary, the present results showed that proactive and retroactive sources of interference can have an appreciable impact on memory performance in rats. Furthermore, the influence of these factors can be very specific in terms of an effect on primacy or recency alone, or on the delay-dependent as opposed to delay-independent aspects of memory performance. Given that both retroactive and proactive interference influence memory performance, the manipulation of them provides a valuable and somewhat novel tool for exploring the effects of lesions on memory in greater detail.

Interaction Between Lesions and Interference

In terms of a comparison of the DMTS performance in lesioned and nonlesioned rats, most of the research relevant to an examination of retroactive interference effects was conducted in Experiment 3.3. Part one of the research examined the effect of food reinforcers in the delay on rats from with large or small MS lesions group, MB group and in the sham-control group. Despite earlier indications (from Experiment 3.1) that food in the delay may result in a separation of groups, the results of Experiment 3.3 showed that although reinforcers placed in the delay were indeed disruptive to performance (reflected in a decrease in delay-independent measures of performance), there was no differential effect across groups. Furthermore, in a second part of the research with a new group of rats, a specific behavioral response requirement (DRL 4 s) in the delay did not differentially disrupt rats which had received a large MS lesion. Consequently, the present results did not confirm the possibility that MS-lesioned rats might show a greater susceptibility to retroactive interference.

The lack of interaction between lesion effects and retroactive interference has implications for the interpretation of both human memory deficits and the basic lesion

effects in the DMTS and SPR tasks. Firstly, although MS damage is a feature of AD and KS neuropathology and MB damage is an aspect of KS neuropathology, the present results were not consistent with the suggestion that damage in either structure plays a significant role in the heightened susceptibility to retroactive interference observed in AD and KS subjects. Secondly, the present results were not consistent with the possibility that retroactive interference could account for impaired performance either following MS damage in the DMTS task or following MS or MB damage in the SPR task. That is, the increase in rate of forgetting observed in the large MS group was not further influenced by the presence of retroactive interference. Consequently, it does not seem likely that the increase in the rate of forgetting shown by this group was due to heightened sensitivity to naturally occurring retroactive influences in the basic DMTS task (e.g. centering the subject by requiring rear lever responding during the delay). Furthermore, other lesion groups were not shown to be more greatly sensitive to such retroactive disruptors in the DMTS task. Thus, arranging for greater levels of retroactive interference in the DMTS task did not result in the obvious performance disruptions that were observed following relatively small MS lesions in the SPR research. Therefore, it appears unlikely that the small MS group displayed a relatively greater disruption to performance at the primacy end of the SPE because of the potentially greater levels of retroactive interference from the presentation of later list items.

In contrast to the lack of interaction between lesion effects and retroactive sources of interference were the significant effects of proactive interference. Whereas different lesion groups all showed the same susceptibility to sources of retroactive interference, the large MS group was markedly more affected than the other groups by proactive interference. Thus, enhanced susceptibility to this source of interference may indeed be critical in accounting for the performance impairments observed following large MS lesion surgery in the DMTS task and following MS lesion surgery in the SPR task. The increase in rate of forgetting following large MS surgery may have been the product of an increased sensitivity to the interfering effects of an immediately previous trial which

was different from the stimulus in the current trial. In particular, responding to the opposite lever or even simply presentation of the other lever as the stimulus in the previous trial resulted in a greater rate of forgetting, relative to trials in which previous stimuli or responses were the same. This source of influence on accuracy was greatest for the large MS group, and was not ameliorated by the increase in ITI.

Such increases in the rate of forgetting resulting from previous trial events may not only account for the increased rate of forgetting observed in overall accuracy observed following large MS surgery but is also consistent with the general reduction in accuracy observed across all serial positions for the small MS group in the SPR study. Experiment 2.3 identified that overall accuracy was reduced in the small MS group particularly due to poorer performance in later trials of the session. That is, exposure to a number of stimuli (some being list arms, some being non-list arms) during early trials may have interfered with performance on later trials in rats with MS damage. To summarise - the increase in rate of forgetting in the large MS group in DMTS may be due to increased sensitivity to disruptive events on previous trials. As noted above, the increase in the rate of forgetting following MS damage can account for the loss of the primacy effect in SPR because items occurring early in the list have a greater period of delay between initial presentation and being tested. Furthermore, increased sensitivity to the build up of proactive interference from previous trials accounts for the general reduction in accuracy across all serial positions following MS damage in the SPR study. Thus, heightened sensitivity to proactive interference appears to account for all the major performance deficits seen following MS damage in Chapters 2 and 3. As will be discussed below, these findings have implications for, firstly the nature of the memory impairments in AD and KS, and secondly, the findings of other various lines of research relevant to the role of the MS in memory.

Before examining some implications of the present findings some concerns need to be raised. There are several findings which are not entirely consistent with the possibility that MS damage results in an increased rate of forgetting due to heightened

sensitivity to proactive interference. Perhaps the most problematic is the lack of influence of proactive interference on the rate of forgetting in the small MS group in the DMTS research. In many ways the small MS group was very dissimilar to the large MS group. While the large MS group displayed a greater sensitivity to 'previous-different trials' than either the MB or sham groups, the small MS group displayed relatively little influence of previous-different trials on the rate of forgetting. Indeed, the rate of forgetting for the small MS group tended to be less over the range of ITIs examined than was the case for all other groups. Also, the small MS group appeared to be largely uninfluenced by previous events in terms of the rate of forgetting and were even less sensitive to these events than the control and MB groups. Such a lack of influence of proactive interference on the rate of forgetting in the small MS group is thus hard to reconcile with the results of the large MS lesion group. Given that the difference between the small and large groups was one of the degree to which damage was caused, it would surely be expected that a greater degree of impairment would be observed in the large MS group but that the small MS group would still display an impairment relative to the other groups.

Finally, although the increase in rate of forgetting for the large MS group was suggested above to be the result of an increase in the sensitivity to previous trial events, these two findings in the large MS group may seem paradoxical with one another. Specifically, given that MS rats forget events more quickly on any given trial then surely previous trials would be expected to have less of an effect on future ones. However, if previous trials were less influential following large MS surgery then according to the current account, there should be no increase in the rate of forgetting. One possible way out of this catch is to suggest that the subjects are not actually 'remembering' discrete events from previous trials but rather are exhibiting a perseverative tenancy to return to a certain location and this perseverative tendency becomes greater at long delays. However, this second possibility can be quickly discounted because a consistent tendency to return to the same location across trials is partialled out in the calculation of *Log d*. In addition, if one were to hypothesize that

the perseverative tendencies were more local in nature, that is 'return to a location or stimulus seen on the immediately previous trial', then the perseverative tendencies necessarily imply the existence of memory for trial by trial events and the whole argument becomes tautologous.

A second possible way to explain the simultaneous existence of high levels of proactive interference with a greater rate of forgetting is to hypothesize that memory for what happened on a previous trial is in some way different from memory during a trial, and that MS damage only alters memory functioning important for accurate performance during a trial. Such a division of memory function is consistent with a division of memory into a number of relatively long-term processes, which do not rely on the transfer of information from a more short-term store or process, and that short-term process itself, (e.g. Baddeley, 1986). For example, MS damage may impair 'explicit' memory for events from both the previous and current trials, but 'implicit' memory may be left intact. According to Baddeley (personal communication) explicit memory may serve as a reminder or checking function with respect to 'what to do next' or 'what has just happened', whereas implicit memory can be shown to be largely independent of such processes and involves memory for procedures. Therefore, although subjects may not remember the act of choosing or seeing a certain stimulus on a previous trial, they may still be influenced by such events and damage to the explicit memory system (and thus impairment to the system which controls the influence of interference) will make them more vulnerable to the potentially disruptive influence of implicit memories.

A third possibility which overcomes the seeming paradox of greater forgetting in conjunction with high susceptibility to previous trial events lies in an interpretation of proactive interference effects, not in terms of the ability to remember the events themselves, but rather ability to remember the 'order' of events. It may be that at long delays there is greater confusion between events which occurred on the previous trial and those which occurred at the start of the current trial, rather than actual memory for

those events decaying more rapidly. With a 5 s ITI and a 5 s delay, there is a total of 10 s between the last choice response and the current choice response and 5 s between the current stimulus presentation and choice. In this case previous trial events may be highly discriminable from current trial events because, although they both occurred recently, the previous-trial response is twice the interval of time in the past compared to the when the present stimulus was presented. But at say a 5 s ITI and 30 s delay there is 35 s interval between the choice on the last trial and the choice on the current trial, compared with a very similar 30 s delay between current trial stimulus presentation and choice. Therefore, discriminating events from the previous and current trials at the point of choice in the current trial may be relatively difficult, and thus accuracy poorer, if the previous trial involved the opposite stimulus/response.

This 'order disruption' account of proactive interference effects is consistent with the finding in control and MB-lesioned rats that as the ITI lengthened, the disruptive effect of 'previous-trial-different' events on rate of forgetting lessened. The implication for the large MS group is that such damage increases the rate of forgetting in the DMTS task because it impairs the ability to discriminate between which events belong to the present trial as opposed to a previous trial, and this remains the case even when trials are made potentially more discriminable by the presence of long ITIs. Thus, the observed effect on the rate of forgetting in the large MS group may have been the result of a reduced ability to remember the order in which recent events have occurred. Further support for the idea that MS damage impairs the ability to remember the order of events comes from studies which require subjects to remember a sequence. For example, T-maze alternation and the 8-arm maze SPR task which uses arm order as stimuli (as used by Kesner and colleagues, see Experiment 2.3) have both been shown to reveal severe disruptions in performance following MS damage (e.g. Kesner, 1988a,b; Rawlins & Olton, 1982). Future research may therefore consider exploring the effects of MS damage in tasks which manipulate the amount to which subjects need to attend to the order of events.

The 'order disruption' account of proactive interference effects in the DMTS research is also to a large degree consistent with the effect of MS damage on SPR performance. Experiment 2.3 found that although control and MB-damaged rats do not show an effect of proactive interference (probably because of the relatively long 20 min ITI in this task) there was a very pronounced effect in the MS group. That is, rats with MS damage showed a general reduction in accuracy for trials late in the session compared with earlier ones, irrespective of list position. These subjects also showed a reduction in the primacy effect which, as suggested earlier, can be accounted for in terms of an increase in the rate of forgetting (which in turn, according to the DMTS results, appears to be the result of an increased susceptibility to proactive interference). However, the current explanation of proactive interference effects is unable to account for the observation that the recency effect was retained following MS damage. The additional delay between the presentation of stimuli at the 'primacy' and 'recency' ends of the sequence is relatively small compared to the ITI in the SPR task. Thus, given that the primacy effect was removed entirely, it might be expected that the recency effect should be removed as well. One possibility is that perhaps, exposure to a number of list items occurring early in the list serves as a prompt that a new trial has begun. Thus late list items, but not early ones, are recognised more accurately because they more clearly belong to the current-trial stimuli.

Irrespective of how proactive interference may come to exert its influence on performance, the present findings indicate that a promising avenue for future research is to determine the extent to which proactive interference accounts for, or at least strongly influences, the performance deficits shown in the variety of tasks which have revealed MS lesion effects on memory (e.g. T-maze alternation, Morris water maze and radial maze tasks).

Implications for Understanding the Neurological Basis of Memory Impairments in AD and KS.

The present effects of large MS lesions in DMTS and small MS lesions in SPR show a great deal of similarity to the memory impairments observed in AD and KS using analogous tasks. MS damage has been implicated in both disorders (Arendt et al., 1983; Antuono et al., 1980) but MB damage has only been implicated in KS (e.g. Mayes et al., 1988; Mair et al., 1979). Therefore, given that there is a great deal of overlap in the memory deficits observed in AD and KS, of the two lesion types examined here the MS rather than MB damage might be expected to result in similar memory impairments to the impairments seen in these human subjects. Indeed, the present studies produced evidence that MS damage results in a loss of the primacy effect in a manner analogous to that observed in both AD and KS subjects (e.g. Miller, 1972; Gibson, 1981; Baddeley & Warrington, 1970; Adelstein et al., 1992). Also, the present DMTS research demonstrated that proactive interference was particularly influential in rats with relatively large MS damage. Similarly, AD and KS subjects show a tendency to be highly influenced by previous exposure to test stimuli (e.g. Delis et al., 1990). Therefore, the MS may be important area of damage in AD and KS with respect to a general sensitivity to proactive interference in these disorders. In turn, MS damage in AD and KS subjects may account for the greater rate of forgetting observed in these disorders shown by a number of studies (e.g. Sahakian et al., 1988; Oscar-Berman & Bonner, 1989; Hart et al., 1988), as well as providing a possible account for the loss of the primacy effect. However, there are a considerable number of studies which question whether there is a greater rate of forgetting in AD and KS, or whether the impairment is better characterised in terms of a delay-independent process (e.g. Money et al., 1992; Kopelman, 1991). Hence, there is still some disagreement in the human literature regarding the actual memory impairments themselves. Consequently, any conjecture regarding the role of MS damage in these disorders will require further investigation of AD and KS memory performance. For example, a study investigating the influence of previous trials on DMTS performance over a range of ITI values, as

done here, may be particularly informative about proactive interference effects in AD and KS subjects.

Irrespective of whether there is a greater rate of forgetting in AD and/or KS, the present results suggest that when MS damage is present (as it is in these disorders) then there will be an increased sensitivity to proactive interference and thus, as described earlier, there are two possible mechanisms by which previous events come to influence current memory performance. Firstly, AD and KS subjects may have impaired memory for explicit events, but intact memory for implicit events and it is via the implicit memory of previous stimuli and choices that memory performance is disrupted. Consistent with this suggestion, there are a number of findings with both AD and KS subjects which show that although these subjects are impaired on various recall or recognition tasks, they often show no or only mild impairments in memory for procedures (e.g. Butters, 1984; Brown & Marsden, 1988) and performance on memory tasks designed to assess implicit memory, such as priming or word completion tasks (e.g. see review by Morris & Kopelman, 1986). A second possibility is that proactive interference in AD and KS has its influence via a disruption in the ability to order the occurrence of previous episodic events. Thus, subjects may become confused whether the correct answer is X or Y, because although they remernber both, they do not know which is correct for the current case. However, with these subjects such a disruption is likely to be limited to the ordering of explicit events given the finding that procedures are still capable of being learnt. Although it is hard to envisage a task in which the order of events is not important in some sense, this interpretation of proactive interference effects following MS damage is consistent with the severe deficits AD and KS subjects show on tasks which rely heavily on the ability to remember order (e.g. SPR for the order of events as used by Kesner and colleagues - Kesner, Crutcher & Measom, 1986; and recall of a sequence of Corsi blocks - Kopelman, 1991).

In contrast with the proactive interference findings, the absence of a greater susceptibility to retroactive interference following either MS or MB damage was a

finding which was largely dissimilar to that obtained with AD and KS subjects. Several studies have shown that in both disorders the presence of events during a delay period severely impairs performance (e.g. Morris, 1986; Sullivan et al., 1986), although there is some debate whether this disruption is a delay-dependent or -independent one (see Section 1.1.1). Irrespective of the manner in which retroactive interference may influence behavior, the lack of effect due to either MS or MB damage in the presence of a variety of retroactive interferers strongly suggests that neither the MS or MB areas, at least on their own, are involved in this feature of the memory deficits in AD and/or KS. Although, it remains to be determined whether a combination of structures (perhaps including either the MS or MB) need to be damaged in order to result in the heightened susceptibility to retroactive interference seen in AD and KS.

Neurological Mechanisms Underlying MS Lesion Effects on Memory

Apart from implications for understanding the neurological basis of the memory impairments in AD and KS, the present results along with much of the previous research remains consistent with the conclusion that MS damage has its effect on memory via a disruption to acetylcholine activity in the HF. To recap, a major projection of the MS area is the HF (Swanson, 1984). At a neurochemical level, neural activity between the MS and the HF is regulated by the neurotransmitters acetylcholine (Wainer et al., 1985) and GABA (Kohler, Chan-Palay & Jang-Yen, 1984). As discussed in Section 1.2.4, a large number of studies have implicated the HF in memory function, although there is very little in the way of general consensus about how to characterise the memory processes that are lost or spared when the HF is damaged (see Sutherland & Rudy, 1989; Squire, 1992; Morris et al., 1986; Rasmussen et al., 1989). Also interruption of the fimbria-fornix, which connects a number of structures to the HF (including the MS and MB) reliably results in memory disruptions (e.g. Olton et al., 1978; Olton et al., 1979; Olton et al., 1989; Dunnett, 1985; Etherington et al., 1987; Aggleton et al., 1991). Furthermore, cholinergic-rich embryonic transplants into the HF of rats have been shown to be successful in restoring impairments to maze-memory performance lost following fimbria-fornix damage (Dunnett et al., 1982). Therefore,

much of the previous lesion research indicates that damage to the MS results in memory impairments because of a disruption in acetylcholine supply to HF.

The possible influence of MS damage on hippocampal function via a disruption to cholinergic activity appears to be consistent with many of the effects of anticholinergic drugs on memory (although a major exception to this consistency will be raised later). For example, the reduction in primacy resulting from scopolamine administration to humans (Crow et al., 1973; Frith et al., 1984) is a pattern similar to that observed in AD, KS and in rats with MS damage. Also, Givens & Olton (1990) demonstrated that microinfusion of scopolamine into the MS area disrupts performance, in a dose dependent manner, in a T-maze alternation task. Finally, the critical role of MS - hippocampal acetylcholine activity is also suggested by the observation that while anticholinergics disrupt memory in a variety of species and tasks, relatively discrete damage to the cholinergic aspects of the NBM (a major contributor of cortical acetylcholine) does not appear to disrupt memory (Markowska et al., 1990; Wenk et al., 1989; Robbins et al., 1989). At this point a warning must be sounded about using the failure of NBM lesions as a line of evidence to support the role of MS lesions in memory. Firstly, because although the MS and NBM regions are the two major sources of CNS cholinergic projections, numerous other smaller cholinergic pathways exist throughout the CNS. Secondly, many of the comparisons performed in the NBM region using relatively more or less cholinergically-specific toxins have not been performed in the MS. As noted earlier, although such a comparison would have been desirable here, it was not possible to refine the surgical procedures with either Quisqualic or Ibotenic Acid to a point at which such comparisons were possible.

Consistent with the role in memory function of the acetylcholine septo-hippocampal connection was the high correlation between hippocampal acetylcholine disruption and the amount of increase in *b* (rate of forgetting) pre- versus post-surgery in the present DMTS research. Using all 20 rats which received MS surgery in Chapter 3, the amount of dorsal hippocampal AChE depletion estimated in the histological analysis was

compared using the ratio of pre- versus post-surgery values for *b* and *Log do.* Pearson's Correlation revealed a correlation of -.431 (p=.058) for AChE depletion by rate of forgetting, and a correlation of .237 (p=.314) for AChE depletion by *Log do.* A similar correlation between amount of hippocampal acetylcholine disruption (via MS damage) and memory impairment has been found by Decker et al. (1992). They found that a radiofrequency lesion of the MS produced relatively greater disruption to hippocampal acetylcholine than did a quisqualic acid lesion, and correspondingly the behavioral impairments in a radial-arm maze task and Morris Water Maze were greatest in the radiofrequency lesion group. Future research may therefore profit by continuing to examine the importance of hippocampal acetylcholine disruption when investigating the effects of MS lesions on memory.

In conclusion, the present finding that MS damage results in memory impairments in SPR and DMTS is consistent with the possibility that several relevant, but traditionally separate, lines of evidence are largely in agreement with one another. Thus, these lines of evidence can be successfully integrated by proposing similar mechanisms of action at the neurological and behavioral levels of explanation. Two generalisations are therefore suggested: First, at a neurological level many of the memory disruptions seen in AD, KS, following administration of anticholinergic drugs and following artificially induced MS damage appear to be the result of disruption to the normal cholinergic activity in the HF. Second, at a behavioral level, the resulting influence of HF cholinergic disruption in these subject groups appears to be the result of increased susceptibility to proactive interference. Two mechanisms by which proactive interference may influence memory performance were suggested earlier - via the disruption of explicit memory concurrent with no effect on implicit memory for previous events, or via a disruption in the ability to order the occurrence of previous events. Therefore, the function of the septo-hippocampal system, as a whole, may be characterised either in terms of a role in explicit memory and/or in the ability to order events.

The above conclusions with respect to the functioning of the septo-hippocampal system have a number of implications for future research. Implicit in the conclusion is that an examination of the effects of damage in one part of the system is unlikely to be informative without considering the interactions with other parts of the system. That is, although the MS is implicated in memory, it is only via comparison against other regions (e.g. MB) and a consideration of its interaction with other structures (e.g. HF) that a picture of how the MS might play a role in memory emerges. In addition, future research and theory must consider to what extent the functioning of the septo-hippocampal system can be characterised solely in terms of the mechanisms suggested both at the neurological and behavioral levels. Neither of the roles suggested for the septo-hippocampal system are new. For example, Squire (1992) proposed that the HF is involved in declarative (explicit) memory but not nondeclarative (implicit memory), whilst other theories of hippocampal function have stressed the role of this structure in making temporal judgements (e.g. Rawlins, 1985). However, it is probable that many brain regions, including the HF and structures connected to it, influence a range of seemingly independent behaviors and do so via a number of different physiological mechanisms. Thus, the generalisations and conclusions suggested here need to assessed in terms of the extent to which they are true across the various relevant subject groups and research paradigms.

Inconsistencies and Issues Yet to be Resolved

Despite many indications that the role of the MS in memory function is via its cholinergic projection to the HF, there remain some inconsistencies which need to be resolved. Firstly, although AD and KS subjects show damage in the MS region and a consequent loss of hippocampal acetylcholine, pharmacological replacement of acetylcholine has been largely unsuccessful in alleviating their memory impairments (e.g. Sullivan, Shedlack, Corkin & Growdon, 1982; Kopelman, 1986; Bartus, Crook & Dean, 1987). However, simply replacing acetylcholine or enhancing its performance in the CNS is unlikely to be of much benefit in these disorders because of the multiple sites of damage throughout the brain and it is unclear to what degree the remaining

anatomical circuitry would be able to utilise acetylcholine effectively. A number of nonhuman studies have examined the combined effect of septo-hippocampal damage and the pharmacological enhancement of cholinergic activity. For example, Emerich & Walsh (1990) found that the ganglioside AGF2 administered prior to AF64A-induced damage of the septo-hippocampal system promoted behavioral recovery (i.e. reacquisition postsurgery) of the standard radial-maze task and ameliorated the hippocampal cholinergic reduction. Also, a number of studies have shown that placing cholinergic-rich transplants into the HF or MS of rats may be successful in overcoming the behavioral and cholinergic disruptions seen following damage to the HF or transection of the fimbria-fornix (e.g. Arendt et al., 1989; Dunnett et al., 1985). Thus, there are indications that the enhancement of cholinergic activity following MS - hippocampal damage can restore prior levels of function.

The conclusion that reductions in hippocampal acetylcholine activity might have resulted in the observed increase in rate of forgetting for rats with MS damage is to some degree inconsistent with the effects of scopolamine on DMTS performance in rats. A number of studies have shown that scopolamine decreases DMTS accuracy and it does so in a delay-independent fashion (e.g. Kirk et al., 1988 and the reanalysis of Dunnett, 1985 in Section 1.3.2). Whereas relatively more specific reductions of hippocampal cholinergic activity via fimbria-fornix lesions (which disconnects the input from the MS to the HF) e.g. Dunnett (1985), or via relatively large amounts of damage to the MS itself (i.e. the present research) both effect DMTS performance in a delay-dependent manner. Given that pharmacological disruption is unspecific in terms of its locus of action, the degree to which these two lines of evidence might be expected to agree remains uncertain. However, both lines of evidence are certainly consistent with the more general conclusion that hippocampal acetylcholine is important in memory function.

Because the MS region also contains cells that are involved in the supply of GABA to the HF, it is possible that acetylcholine disruption is not responsible, or is only partly

responsible, for the memory disruptions observed following MS damage. Therefore an issue that requires further investigation, is whether disruptions to GABA activity were responsible for the changes in the performance impairments following MS damage in the present research. However, there is some evidence already which indicates that the disruption to hippocampal acetylcholine rather than disruption to hippocampal GABA may be more critical in memory disruptions following MS damage. Peterson & McGinty (1988) reported that infusion of the neurotoxin colchicine into the lateral cerebroventricles of rats had a relatively specific effect on cholinergic neurons in the MS, while sparing GABAergic ones. Barone et al. (1991) found that such ventricular infusion of colchicine resulted in an interference with Morris Water Maze task acquisition. However, Barone et al. (1991) also found that direct infusion of colchicine into the MS area produced similar disruptions to hippocampal acetylcholine without concurrent disruption to task acquisition. Thus the role of GABA remains unclear and the nonspecific effects of intraventricular colchicine infusion will need to be further determined before ruling out the role of neurochemicals other than acetylcholine in Barone et al's research. In addition, the comparative effects of cholinergic and GABAergic disruption on memory are best assessed using more direct measures of memory performance than task acquisition.

Should it turn out that MS GABAergic activity is important in the MS lesion effects on memory then it becomes unclear how anticholinergic drugs exhibit an influence on memory task performance. One way to reconcile the possibility that neither the MS - hippocampal acetylcholine nor NBM - cortex acetylcholine pathways are critically involved in memory performance with the observed effects of anticholinergics on memory is to suggest that a general reduction of acetylcholine throughout the CNS is necessary to disrupt memory function. That is, acetylcholine disruption via damage solely in either the MS (the present research) or NBM areas (e.g. Markowska et al., 1990; Wenk et al., 1989; Robbins et al., 1989) is insufficient to cause memory task impairments. Consequently, it could be that concurrent damage in both the MS and NBM may result in a delay-independent reduction in accuracy in DMTS performance,

as appears to be the case following scopolamine administration. Whereas, relatively specific disruptions to MS-supplied GABA may result in the increase in rate of forgetting observed with the large MS group.

Another issue that will need to be dealt with in future research is the effect of manipulations to multiple anatomical sites and chemical pathways. No one brain region is responsible for all memory function and the range of neuropathology in neurodegenerative disorders such as AD and KS suggests that disruptions to memory function may come about through damage to combinations of brain regions rather than single sites. For instance, as suggested above, damage in multiple basal forebrain regions (e.g. NBM and MS) or multiple sites of damage afferent and efferent to the HF (e.g. MS, entorhinal cortex and MB) may be required to produce the severe memory disruptions observed in such disorders. Furthermore, an understanding of the neurological bases of learning and memory will require further investigation regarding the interactions of various neurochemical pathways (such as noradrenaline and serotonin) which have also been implicated in memory.

Conclusions

There is some way to go experimentally before a clear picture will emerge of memory function at both the behavioral and neurological levels of explanation. However, taking an approach which stresses the importance of analogous tasks, such as adopted in the current research, allows for some consistency across experiments and species, and thereby enables the simultaneous and congruent examination of both behavioral and neurological variables in memory.

The starting position of the present research was that the investigation of brain regions connected to the HF, and in particular those regions involved in the supply of acetylcholine to it, was likely to show that these regions are involved in memory function. Further, that the examination of the interaction between lesion effects and interference was liable to be informative with regards to the nature of any memory

impairments. The present research demonstrated that the role of the MB, a brain region anatomically connected with the HF but not part of its cholinergic supply, is equivocal with respect to memory function. In contrast, and in accord with initial expectations, the present results are consistent with the thesis that the MS is critical in memory function via its cholinergic input to the HF, and damage in this structure results in a variety of memory impairments which are manifest in a greater susceptibility to the disruptive effects of proactive interference. Thus, in answer to the two questions posed at the start of this chapter: 1) Yes, there are differences in the effects of MS and MB damage on memory performance and specifically MS damage is more disruptive than MB damage. 2) The present research appears to be in accord with much of the evidence from both human and nonhuman research which indicates that the MS region is a critical area of importance in normal memory function.

I do hope you enjoyed reading my thesis ..... almost as much as I enjoyed finishing it !!!

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APPENDICES

Appendix A: Histological Analysis

At the end of Experiment 2.3 and Experiment 3.3, subjects were sacrificed, perfused, and brains were removed for storage in 4% formaldehyde followed by a 30% sucrose-formalin solution. Two series of frozen coronal sections (25 μm thick) were taken. One series was taken through the rostrocaudal extent of the medial septum. Every third section was mounted on a glass slide, which was then stained with cresyl violet. The size and location of the lesions were assessed by microscopic examination for the loss of neurons and the presence of gliosis. The other series of sections was obtained through the rostrocaudal extent of the hippocampus. Every third section was mounted on a glass slide, which was stained for the presence of acetylcholinesterase (AChE) to examine the extent of cholinergic AChE. The sections were incubated overnight in a solution containing cupric sulfate, glycine, ethoproprazine and acetylthiocholine iodide and subsequently developed with sodium sulphide and enhanced with silver nitrate.

The extent of dorsal hippocampal AChE depletion from the rats in Experiments 3.1 to 3.3 was scored by visually comparing the degree of staining in the dorsal hippocampus (for both hemispheres separately) in all lesioned animals against a standard control. The degree of AChE depletion was graded from 0 to 10, with a score of 0 representing no staining present and a 10 representing no reduction in AChE staining. The rats from the SPR experiment (Experiment 3.2) were not scored in this way because, of damage to a number of slides during processing.

MS AND MB DAMAGE FROM EXPERIMENT 2.3

All 10 rats in the medial septal group demonstrated appropriate damage to the medial septum area and all 6 rats in the MB lesion group displayed damage to the mammillary body region. One rat from the MB group displayed damage located primarily in the lateral mammillary nuclei. All rats displayed some damage to the posterior medial mammillary nucleus and all but two showed some damage in the supra mammillary region. Figures 5.1 and 5.2 show the extent of damage for the individual with the smallest (shaded) and largest (grid-lined) MS and MB lesion in each group, respectively. The cholinergic AChE in the hippocampus for a representative rat from the MS and MB lesion groups is shown in Figures 5.3 and 5.4, respectively. The AChE sections for 1 MS rat were lost during processing. For the remaining 9 MS rats, there was an observable but incomplete bilateral reduction in AChE relative to the 5 MB lesioned rats. For six of the MS rats, the hippocampal AChE reduction was asymmetric.

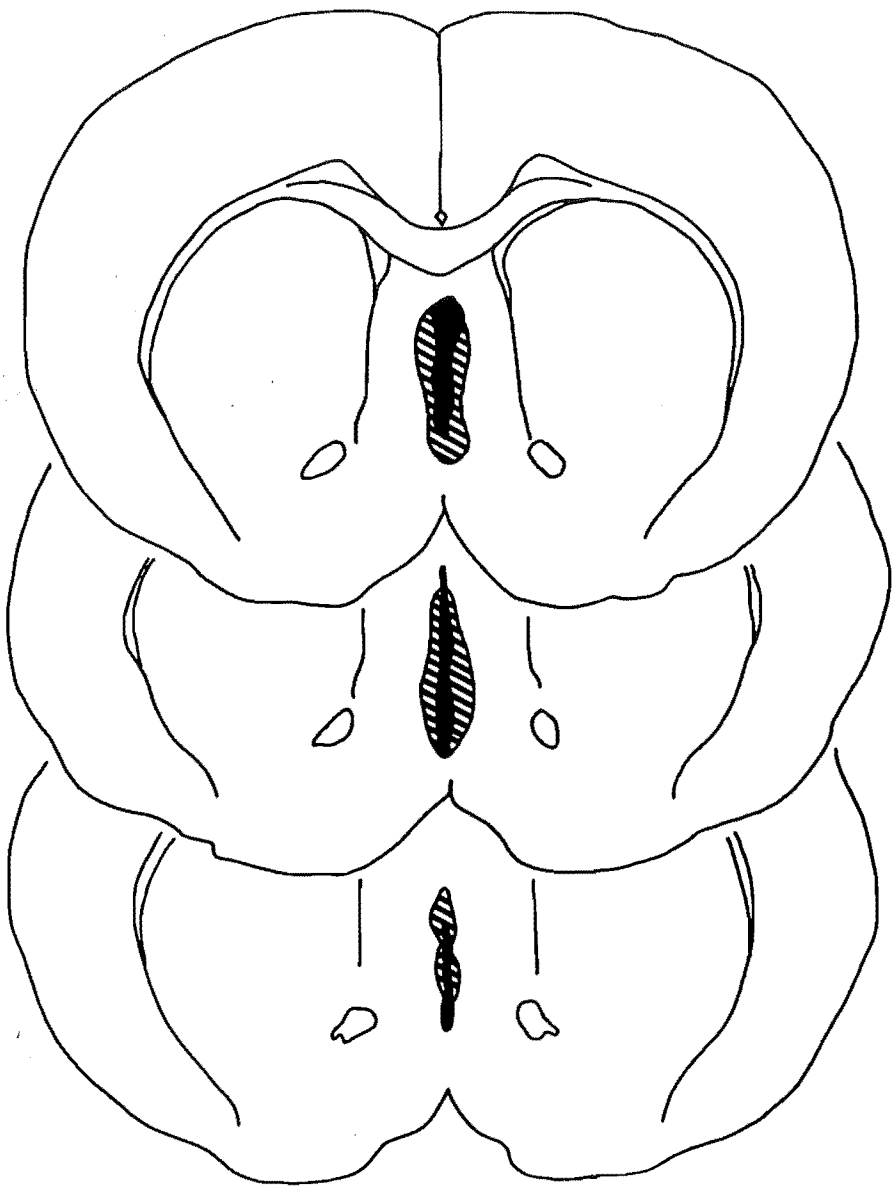


FIG 5.1 Schematic representation of the largest (shaded) and smallest (grid) MS lesion reconstructed from cresyl violet stained sections. Slices are organised anterior (top picture) to posterior (bottom); 0.7, 0.48 and 0.20 mm anterior to bregma (Paxinos & Watson, 1986).

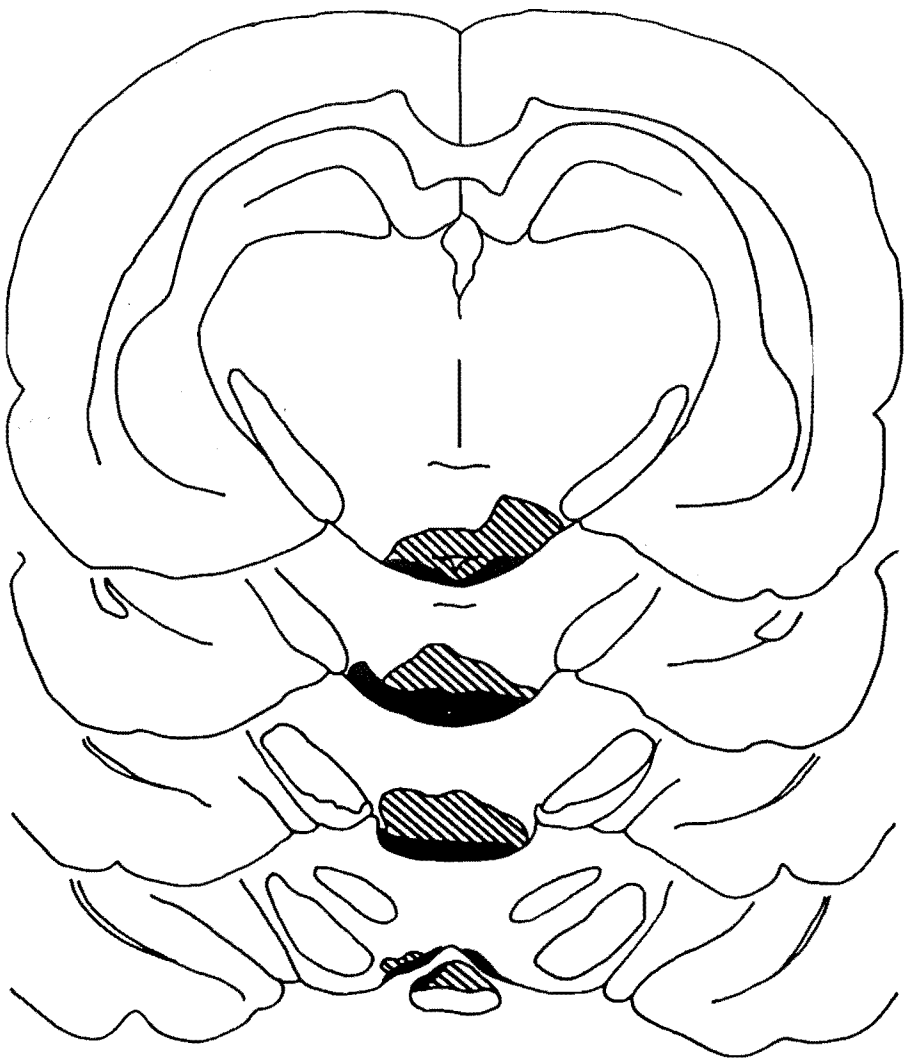


FIG 5.2 Schematic representation of the largest (shaded) and smallest (grid) MB lesion reconstructed from cresyl violet stained sections. Slices are organised anterior (top picture) to posterior (bottom); -4.30, -4.52, -4.80 and -5.20 mm anterior to bregma (Paxinos & Watson, 1986).

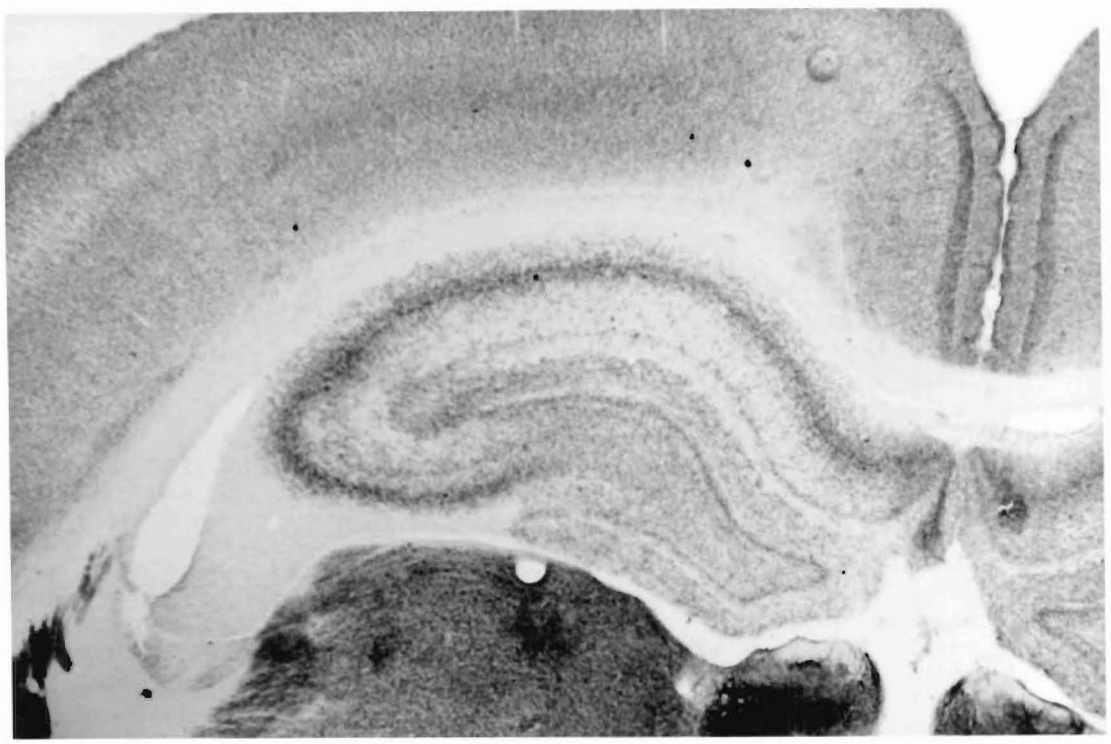


FIG 5.3 Degree of cholinergic inervation in the hippocampus as revealed by AChE histochemistry for a typical animal from the MS lesion group.

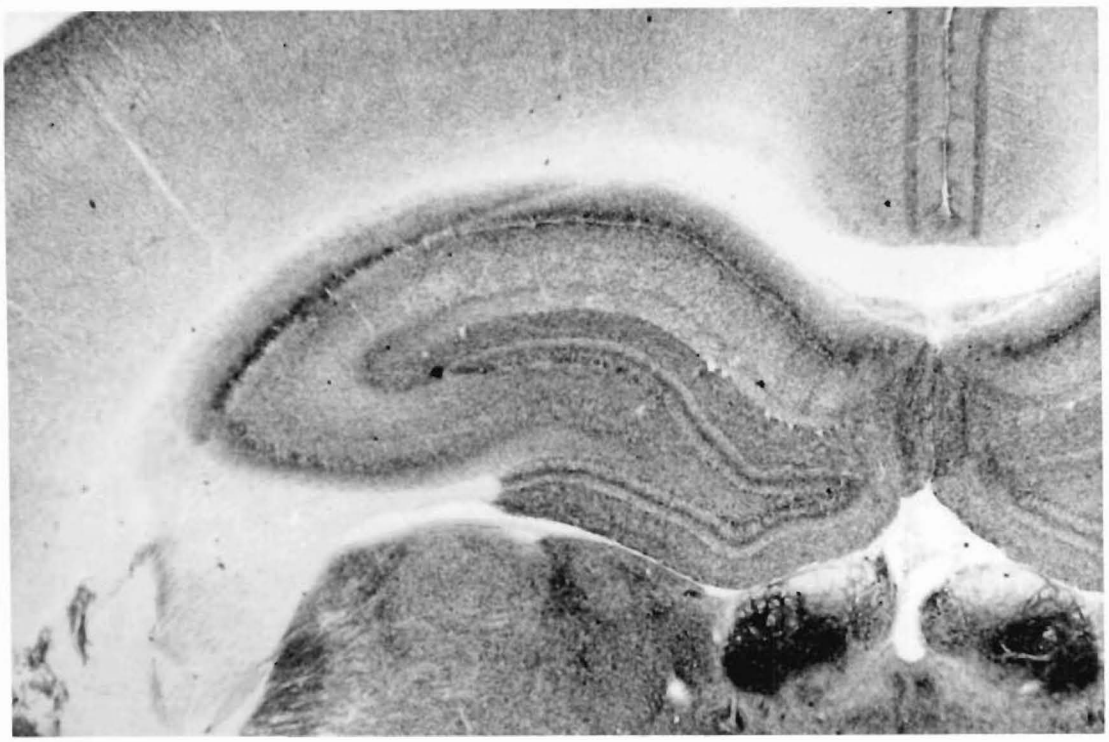


FIG 5.4 Degree of cholinergic inervation in the hippocampus as revealed by AChE histochemistry for a typical animal from the MB lesion group.

MS AND MB DAMAGE FROM EXPERIMENTS 3.1 - 3.3

In all, 4 groups of rats received actual lesions in Chapter 3 of the research - 1 group received relatively small MS lesions, 1 group received a MB lesion and 2 groups received relatively large MS lesions. All 8 small MS rats displayed appropriate damage that was restricted to the MS region (see Figure 5.5). Similarly, for the 7 MB rats there was appropriate damage to the MB region which included the lateral and posterior medial nuclei, and for 4 rats damage extended to portions of the supra mammillary region (see Figure 5.7). Because the same operation was performed on the 2 large MS groups under the same conditions, and comparisons showed that damage was very similar across them, all 12 subjects are combined here for the presentation of histology (see Figure 5.6). One subject was excluded from analysis (G1G) because it did not display damage in the MS, rather damage was located more posterior, in the region of the fimbria/fornix.

The cholinergic AChE in the hippocampus for a representative rat from the small MS, large MS, MB and sham-control surgical groups is shown in Figures 5.8, 5.9, 5.10 and 5.11, respectively. The MB group displayed no reduction in hippocampal AChE relative to the sham group. Both small and large MS lesion surgery resulted in a reduction of hippocampal AChE. The AChE staining for the small MS group was comparable to that observed in the SPR study (Fig 5.3), that is there was a noticeable but incomplete reduction in AChE which was assymetric across the 2 hemispheres for 5 subjects. The mean AChE depletion score, across all 8 subjects, was 5.63 (s.d. 1.73) for the left hippocampus and 7.00 (s.d. 2.59) for the right. The AChE staining for the large MS animals demonstrated that the degree of depletion was greater for all rats in this group than that shown by individuals in all the other groups (except for B1G in the small MS group). The depletion was also more symmetric across hemispheres than observed in the small MS group, that is only 3 out of 12 subjects displayed a noticeable assymetry in AChE staining. The mean AChE depletion score, across all 12 subjects, was 2.92 (s.d. 1.29) for the left hippocampus and 3.58 (s.d. 1.44) for the right.

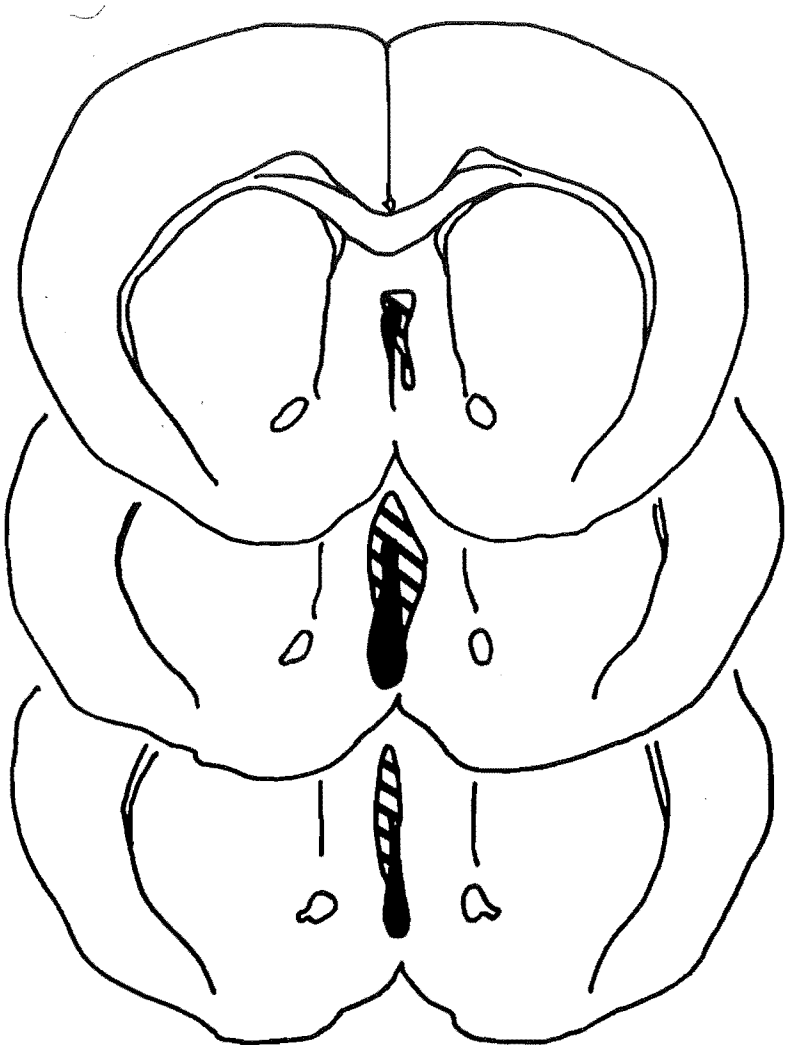


FIG 5.5 Schematic representation of the largest (shaded) and smallest (grid) lesion, from the small MS lesion group, reconstructed from cresyl violet stained sections. Slices are organised anterior (top picture) to posterior (bottom); 0.70, 0.48 and 0.20 mm anterior to bregma (Paxinos & Watson, 1986).

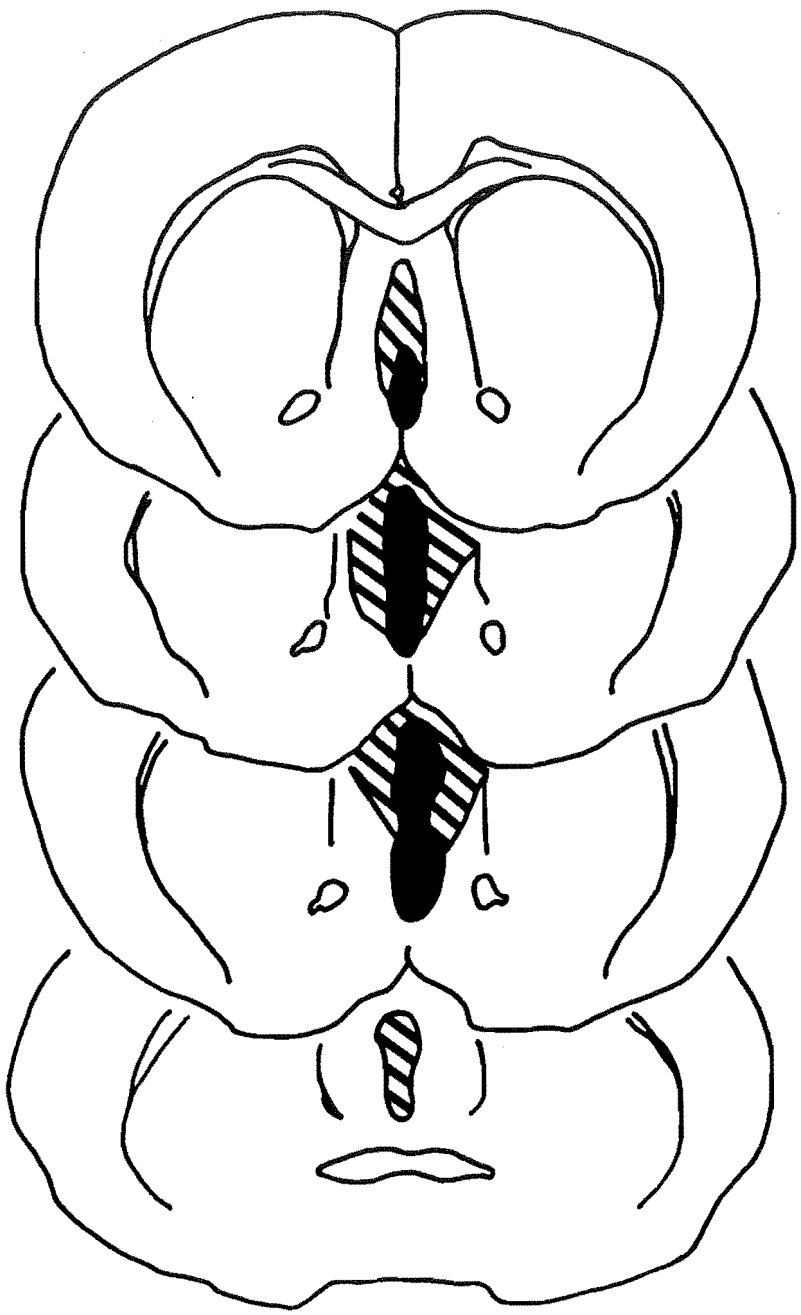


FIG 5.6 Schematic representation of the largest (shaded) and smallest (grid) lesion, from the 2 large MS lesion groups, reconstructed from cresyl violet stained sections. Slices are organised anterior (top picture) to posterior (bottom); 0.70, 0.48, 0.20 and -0.26 mm anterior to bregma (Paxinos & Watson, 1986).

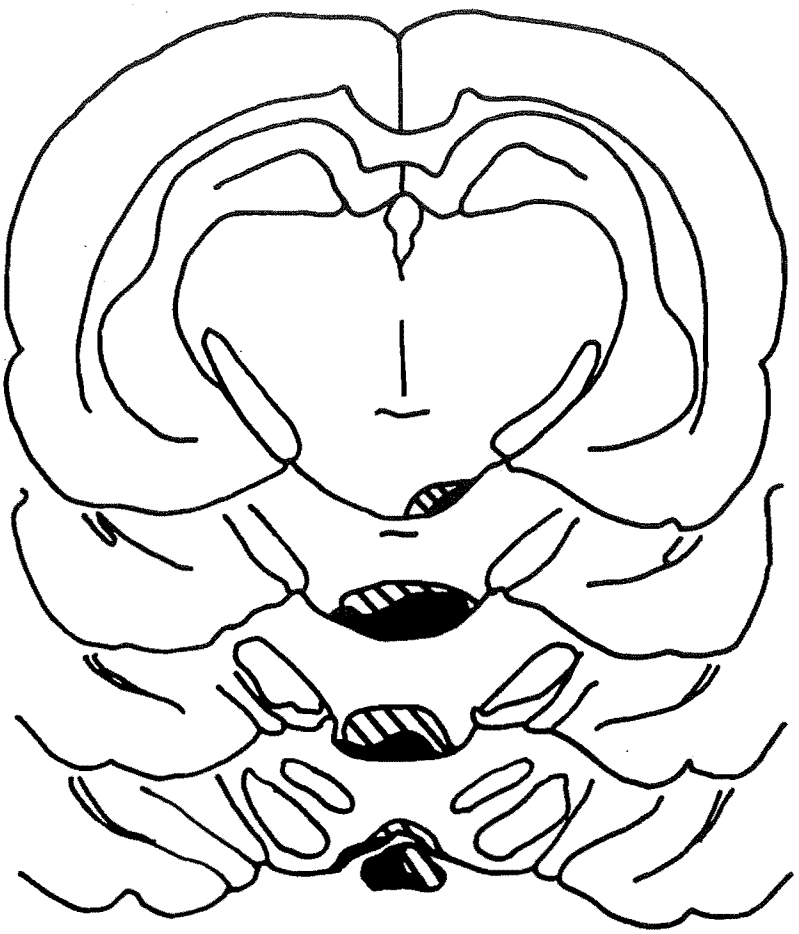


FIG 5.7 Schematic representation of the largest (shaded) and smallest (grid) MB lesion reconstructed from cresyl violet stained sections. Slices are organised anterior (top picture) to posterior (bottom); -4.30, -4.52, -4.80 and -5.20 mm anterior to bregma (Paxinos & Watson, 1986).

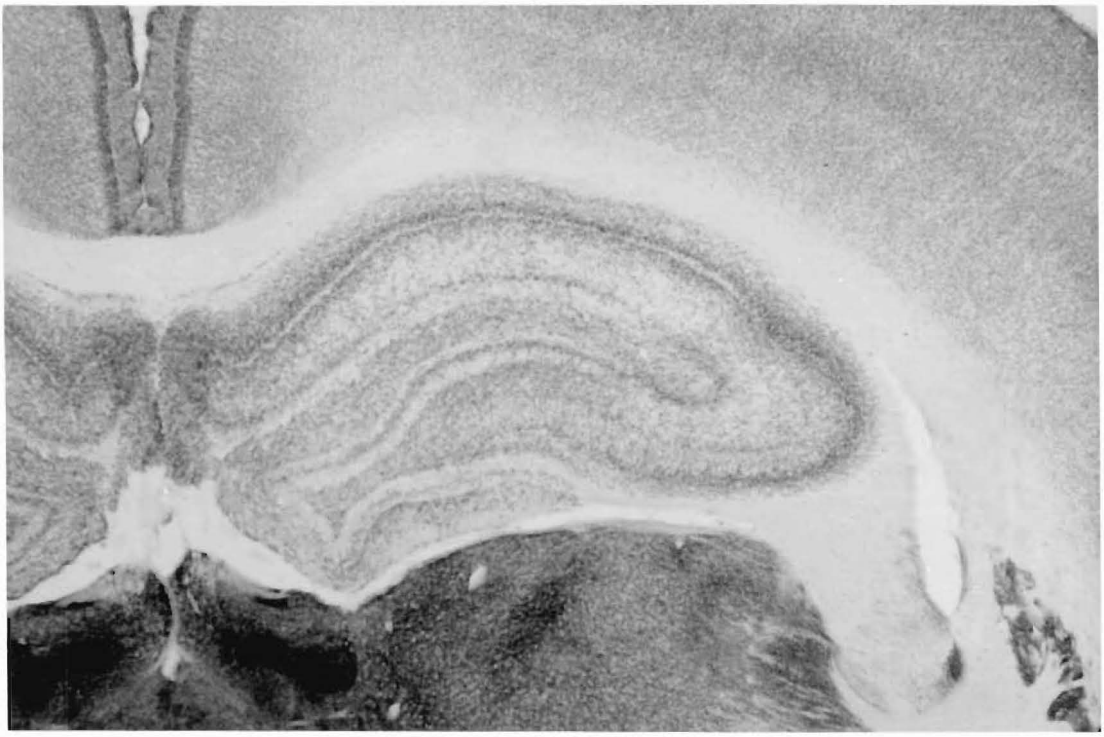


FIG 5.8 Degree of cholinergic inervation in the hippocampus as revealed by AChE histochemistry for a typical animal from the small MS lesion group in Chapter 3.

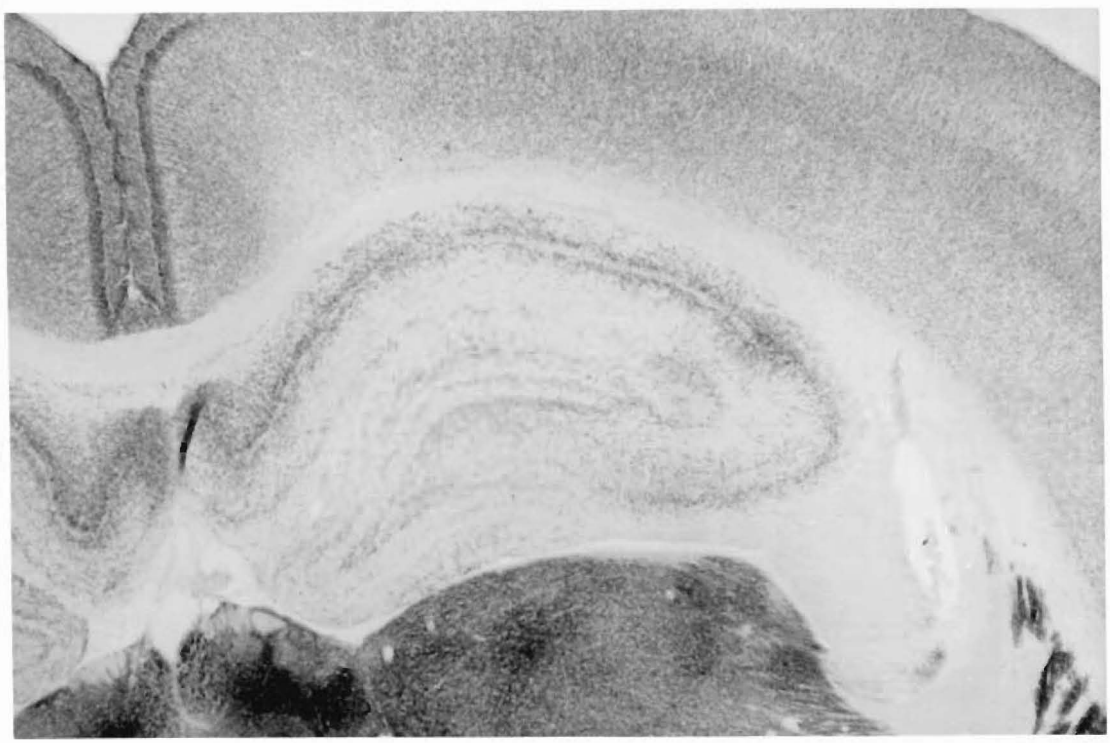


FIG 5.9 Degree of cholinergic inervation in the hippocampus as revealed by AChE histochemistry for a typical animal from the large M5 lesion group in Chapter 3.

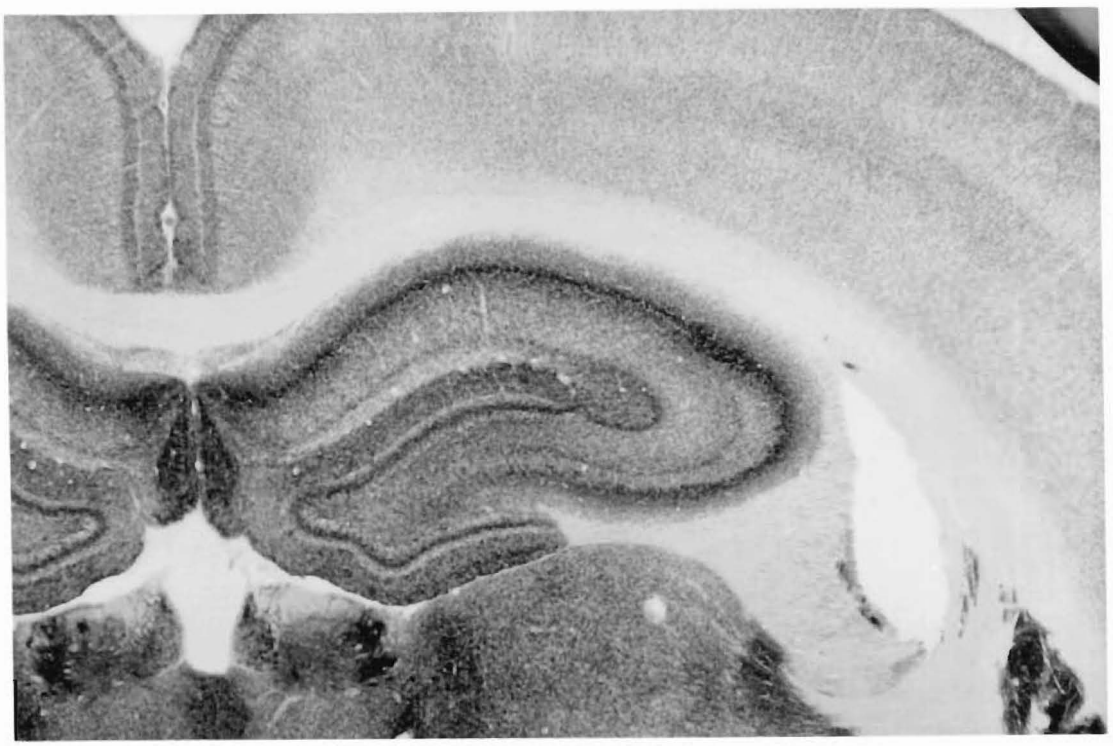


FIG 5.10 Degree of cholinergic inervation in the hippocampus as revealed by AChE histochemistry for a typical animal from the MB lesion group in Chapter 3.

FIG 5.11 Degree of cholinergic inervation in the hippocampus as revealed by AChE histochemistry for a typical animal from the sham-control group in Chapter 3.

APPENDIX B: SERIAL PROBE RECOGNITION DATA FROM CHAPTER 2

EXPERIMENT 2.1

Mean Percent Correct According to Serial Position

	POSITION				
SESSIONS	1	2	3	4	5
sessions 1-6	63.8	65.9	65.2	60.1	60.1
sessions 7-12	79.0	70.3	65.9	55.8	76.1
sessions 13-18	75.4	75.4	70.3	60.1	78.1
sessions 19-24	79.4	74.9	67.3	71.0	83.7
sessions 25-30	82.6	82.6	73.9	68.8	80.4

	1	3	4	5	7
sessions 34-39	78.3	69.2	65.8	62.5	83.3
sessions 40-45	85.8	69.2	70.8	68.3	87.5
sessions 46-51	79.2	63.3	68.3	70.0	93.3

EXPERIMENT 2.2

Mean Percent Correct According to Serial Position and Delay (Part 1).

	POSITION				
DELAY(s)	1	3	4	5	7
5	80.8	68.3	70.0	70.8	84.2
10	85.8	64.2	72.5	70.4	83.3
20	80.0	75.8	68.3	66.7	74.2
30	80.0	63.3	66.7	60.8	72.5
60	63.3	67.5	65.0	63.3	68.3

Log d for Positions 1, 4 and 7 According to Delay (Part 1).

	POSITION		
DELAY(s)	1	4	7
5	0.64	0.37	0.73
10	0.79	0.43	0.72
20	0.63	0.34	0.46
30	0.61	0.30	0.42
60	0.25	0.27	0.34

Mean Percent Correct According Serial Position -

10 s unfilled delay versus free food in 10 s delay (Part 2)

	POSITION				
	1	3	4	5	7
baseline (unfilled delay)	80.8	69.2	75.8	75.8	89.2
free access to food in delay	78.3	67.5	60.0	66.7	62.5

EXPERIMENT 2.3

Mean Percent Correct Pre- and Post-surgery According to Serial Position and Group.

	POSITION				
GROUP	1	3	4	5	7
Medial Septal					
pre.	80	70	73	70	88
post.	54	56	65	62	70
Mammillary					
pre.	75	72	69	72	83
post.	67	65	65	67	68
Sham-control					
pre.	82	68	78	82	90
post.	78	71	68	69	87

APPENDIX C: DMTS DATA FROM CHAPTER 3

N.B. All data in this section are given as response matrices for individual subjects according to each delay (see Figure 1.9), that is:

C1 E1

E2 C2

where C1 and C2, respectively are the total number of correct responses on the left and right lever stimuli made over the entire condition, and E1 and E2 are the corresponding errors.

EXPERIMENT 3.1

Prelesion Response Matrices for Individual Subjects - Parts 1, 2 and 4

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	112	15	55	10	47	14	42	20	42	21
	21	111	11	58	19	47	21	43	33	34
B1B	160	3	82	3	73	7	68	16	68	14
	3	148	12	73	10	74	15	70	18	68
B1G	159	3	78	3	78	3	76	5	74	5
	3	155	9	74	14	67	16	67	14	65
B2R	125	10	58	7	47	21	34	36	40	31
	9	129	6	65	6	60	6	66	9	63
B2B	134	23	64	16	54	23	50	27	45	34
	27	132	11	65	22	59	22	58	19	62
B2G	138	21	71	4	58	22	50	26	55	26
	25	129	20	60	17	61	31	46	30	48
B2W	149	16	70	12	56	28	44	40	36	47
	46	117	22	60	28	56	24	61	20	63
E1R	221	3	110	6	99	11	100	12	100	10
	4	218	3	103	2	105	8	102	18	87
LARGE MS										
G1R	135	32	62	22	40	41	45	38	49	35
	12	154	10	72	6	78	12	71	23	58
G1B	169	4	88	2	80	6	87	3	82	3
	22	153	10	76	7	78	16	71	32	54

G2R	143	24	73	10	65	17	55	31	52	34
	26	145	21	62	31	58	33	50	28	55
G2B	143	19	67	15	72	12	56	26	51	36
	12	154	7	79	12	74	13	72	20	65
G2G	168	2	79	5	66	16	60	23	48	35
	2	163	4	80	22	61	25	60	18	70
G2W	136	26	76	7	76	10	68	13	64	18
	9	155	18	64	25	57	48	36	40	41
MAMMILLARY										
D1R	162	2	78	4	75	4	77	3	76	4
	2	159	1	81	4	76	5	75	5	75
D1B	131	34	65	18	69	11	55	22	56	24
	53	108	27	54	31	50	39	41	42	37
D1G	129	35	64	19	67	12	66	15	68	14
	28	132	15	65	36	45	46	35	56	26
D2R	147	11	74	5	75	8	70	10	71	10
	9	151	10	70	16	64	37	43	38	42
D2B	158	9	79	8	66	16	57	30	56	32
	5	164	3	84	10	77	13	73	14	73
D2G	166	2	82	1	75	7	70	15	72	15
	5	169	7	76	16	66	20	67	23	64
D2W	150	25	54	33	32	51	18	68	24	61
	22	151	14	70	17	66	20	69	18	72
SHAM										
C1R	153	8	80	3	65	14	54	27	38	42
	8	151	3	77	1	82	8	76	2	78
C1G	146	3	67	6	69	5	63	12	60	9
	9	139	8	67	13	65	14	62	18	56
C2R	141	22	65	20	53	29	44	41	38	48
	7	160	19	67	22	64	18	67	17	66
C2B	153	8	75	7	67	15	57	25	54	27
	18	144	20	60	16	64	20	61	26	56
C2G	144	23	78	7	62	20	57	28	52	34
	3	163	3	80	3	81	7	79	18	66
C2W	128	33	57	24	47	34	50	31	41	41
	6	155	2	78	11	69	13	70	9	72

Postlesion Response Matrices for Individual Subjects - Parts 2 and 4

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	108	31	52	14	53	13	53	14	43	28
	8	137	10	60	16	52	18	50	15	57
B1B	163	2	80	6	66	20	66	20	61	23
	13	158	11	75	15	70	27	59	30	56
B1G	158	3	84	1	79	2	80	2	71	9
	2	159	3	77	11	69	86	75	14	68
B2R	155	8	65	14	53	27	47	33	35	46
	3	159	1	80	8	74	6	75	7	73
B2B	139	27	64	20	48	34	32	53	30	57
	29	143	12	75	13	72	9	76	8	77
B2G	158	20	79	8	76	11	63	21	64	23
	34	135	26	61	30	62	37	49	45	39
B2W	158	7	73	11	49	31	35	48	26	59
	33	134	22	61	17	68	17	66	15	69
E1R	170	5	83	6	77	11	71	13	71	14
	6	160	4	81	5	78	18	66	28	57
LARGE MS										
G1R	152	18	53	31	35	48	38	46	44	42
	5	169	3	80	1	85	10	76	25	64
G1B	166	4	79	4	86	2	76	10	79	3
	16	154	10	80	19	62	37	50	49	38
G2R	150	19	65	25	46	40	41	41	41	45
	20	154	8	76	20	67	19	71	19	65
G2B	138	27	47	38	31	54	26	60	29	59
	38	128	13	81	9	79	12	74	20	66
G2G	169	6	78	9	69	21	60	30	47	37
	17	158	10	78	47	38	31	53	33	55
G2W	146	17	63	22	65	20	61	24	63	23
	24	146	19	67	35	52	45	45	56	30
MAMMILLARY										
D1R	161	4	73	7	71	10	70	11	63	15
	3	158	4	77	8	72	5	76	3	77
D1B	106	53	59	22	59	21	60	21	62	22
	45	119	27	51	47	34	47	35	48	31
D1G	111	52	44	35	44	37	40	43	28	57
	17	145	9	70	14	66	14	70	19	62

D2R	143	17	66	14	53	29	48	33	33	48
	2	161	3	78	12	70	8	72	11	72
D2B	166	7	81	4	78	10	68	20	63	23
	3	164	8	83	5	82	14	72	8	77
D2G	171	1	84	3	81	6	77	9	75	10
	3	170	3	84	15	69	18	67	28	60
D2W	171	10	77	16	52	39	29	61	22	63
	45	131	17	69	20	66	19	69	10	72
SHAM										
C1R	155	8	74	9	52	29	44	38	55	28
	8	154	6	76	11	73	8	72	15	69
C1G	143	9	69	6	69	6	69	9	74	5
	4	149	5	71	7	69	12	67	29	50
C2R	128	41	66	19	56	28	46	36	42	41
	10	161	30	58	31	55	35	49	32	52
C2B	159	6	79	3	69	16	63	22	54	28
	19	144	9	73	10	75	19	64	19	64
C2G	169	6	79	7	75	14	74	11	68	21
	4	167	8	81	13	73	21	65	35	53
C2W	149	17	64	18	60	23	53	30	46	39
	7	160	8	79	13	70	10	73	16	65

Postlesion Response Matrices for Individual Subjects - Part 3 - Inter-trial Interval 5 sec.

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	148	23	73	13	68	20	63	20	53	28
	19	147	7	75	13	71	19	65	22	63
B1B	190	3	92	4	85	14	82	16	80	16
	25	172	10	85	24	72	25	73	35	62
B1G	188	3	86	11	90	7	87	12	84	73
	11	186	10	86	23	76	22	77	22	73
B2R	138	36	66	22	57	28	49	39	44	48
	18	81	7	81	13	72	16	72	12	73
B2B	162	37	67	32	64	33	48	49	38	61
	35	160	15	82	17	82	14	85	17	82
B2G	181	19	86	14	81	19	75	25	78	22
	47	153	38	62	39	61	57	43	63	37

B2W	175	25	77	22	57	43	47	53	44	56
	34	166	20	79	27	73	25	75	20	80
E1R	197	3	99	1	99	1	86	14	91	9
	13	187	8	92	7	93	15	85	29	71
MAMMILLARY										
D1R	150	29	85	7	73	14	72	20	65	25
	6	170	5	85	9	80	6	82	5	82
D1B	167	32	88	12	84	15	66	34	63	37
	61	136	56	43	52	48	49	51	49	51
D1G	176	23	64	33	50	50	56	44	36	60
	66	129	33	66	35	64	28	69	30	69
D2R	175	13	84	9	75	20	69	27	62	35
	5	180	12	79	15	79	17	76	21	74
D2B	177	16	93	6	80	18	82	16	79	18
	3	191	1	96	3	94	8	89	6	92
D2G	194	6	92	8	94	6	85	15	83	17
	7	193	5	95	24	76	39	61	49	50
D2W	170	30	85	15	72	28	64	36	63	37
	93	107	51	49	57	43	56	44	50	50
SHAM										
C1R	163	23	70	24	67	28	63	29	48	46
	29	152	15	79	27	66	30	61	25	72
C1G	158	7	81	3	78	9	68	16	63	18
	20	143	11	71	20	61	26	57	26	57
C2R	140	55	74	24	72	28	53	45	65	33
	26	170	31	66	29	68	43	56	53	44
C2B	175	18	90	10	45	52	39	60	41	58
	14	184	10	85	15	84	10	88	20	78
C2G	188	11	89	11	78	22	69	31	78	22
	9	191	9	91	11	88	25	75	39	61
C2W	158	26	71	20	61	34	51	43	43	48
	18	166	12	77	19	73	18	74	13	74

Postlesion Response Matrices for Individual Subjects - Part 3 - Houselight on in middle of delay

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	105	23	49	20	41	23	33	33	35	28
	15	120	9	59	8	59	12	58	15	51
B1B	165	6	80	5	75	7	78	8	69	12
	8	157	5	80	15	70	20	67	30	56
B1G	164	4	80	4	76	8	73	10	70	11
	10	159	7	76	14	67	18	67	21	66
B2R	143	12	72	8	71	8	73	8	68	13
	31	128	15	63	20	62	16	63	21	59
B2B	140	26	76	12	50	33	47	33	43	41
	21	147	15	68	11	72	11	76	18	67
B2G	143	32	62	21	74	14	67	18	71	17
	15	154	17	65	29	61	52	36	66	23
B2W	141	31	68	17	50	37	53	40	37	52
	21	152	15	74	22	62	20	65	28	60
E1R	269	1	133	1	133	2	131	7	114	18
	6	257	8	123	9	118	9	120	11	119
MAMMILLARY										
D1R	150	4	72	5	74	2	74	5	65	10
	3	154	2	76	3	75	6	73	3	74
D1B	143	24	64	20	67	19	64	16	72	13
	33	139	31	54	36	46	51	35	63	23
D1G	149	17	57	28	53	30	47	35	45	38
	36	133	16	67	31	52	36	46	41	44
D2R	152	5	71	8	74	5	78	3	67	15
	6	154	5	75	17	62	23	58	36	45
D2B	171	6	82	4	81	6	79	9	71	15
	2	177	3	82	7	80	8	76	4	81
D2G	171	5	83	6	79	11	77	12	82	5
	4	167	6	83	33	54	30	59	37	47
D2W	142	34	79	14	60	32	60	30	48	43
	30	147	27	60	34	53	27	55	38	49
SHAM										
C1R	143	17	72	10	66	14	65	18	55	27
	4	159	6	74	11	71	15	66	16	65
C1G	124	14	57	12	62	12	58	12	52	16
	13	129	14	53	15	54	17	53	24	48

C2R	151	20	75	7	66	17	67	15	62	18
	20	150	42	45	41	42	36	47	43	39
C2B	143	26	71	12	45	41	36	44	40	43
	1	170	8	77	8	76	23	61	30	55
C2G	172	6	78	12	72	18	63	24	59	28
	4	169	2	88	12	74	21	63	30	54
C2W	153	10	63	18	50	31	46	36	45	40
	12	154	7	74	13	74	23	57	19	62

Postlesion Response Matrices for Individual Subjects - Part 3 - Reinforcer presented at beginning of each delay

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	110	31	54	16	56	15	52	21	47	23
	43	101	13	61	14	63	22	49	21	49
B1B	162	3	79	4	79	8	80	5	76	4
	13	154	6	79	16	72	31	55	32	54
B1G	164	10	82	8	83	4	69	18	69	18
	21	156	14	76	39	45	32	50	22	65
B2R	123	34	54	22	55	25	61	19	54	21
	27	132	11	69	10	67	21	56	17	63
B2B	108	58	56	26	44	41	30	54	21	61
	29	139	12	73	16	67	17	65	15	67
B2G	158	8	80	4	71	13	71	10	72	11
	42	125	25	58	38	44	46	37	59	25
B2W	100	59	50	28	46	37	39	42	26	54
	23	138	19	63	19	63	19	61	12	67
E1R	182	3	95	1	88	4	87	5	80	11
	10	175	4	89	11	84	16	72	25	67
MAMMILLARY										
D1R	153	15	68	15	63	19	61	23	61	22
	12	153	14	68	22	62	25	58	27	55
D1B	158	14	83	4	75	14	72	14	69	17
	11	156	12	74	16	64	25	66	25	68
D1G	153	15	69	15	54	30	53	29	59	22
	30	134	8	77	36	45	44	41	57	32

D2R	139	24	72	8	63	19	61	19	55	25
	19	142	12	68	16	65	19	60	22	59
D2B	133	20	69	9	72	10	61	17	52	29
	8	149	6	73	5	73	12	68	11	68
D2G	160	11	81	6	79	9	76	8	77	11
	8	159	5	82	27	62	34	53	42	47
D2W	145	29	79	9	57	30	58	22	60	31
	59	117	35	49	42	44	49	37	44	43
SHAM										
C1R	147	17	79	6	75	11	75	9	71	14
	5	164	2	85	3	83	9	76	3	84
C1G	151	13	73	14	53	31	51	32	60	24
	29	142	22	63	22	65	34	48	49	34
C2R	118	44	54	26	51	28	50	27	48	33
	23	135	12	69	19	62	28	53	23	57
C2B	141	23	74	10	33	50	24	59	28	55
	5	158	2	83	9	72	13	68	18	62
C2G	146	18	74	12	61	23	57	28	54	27
	20	150	7	76	18	68	28	57	33	48
C2W	125	25	62	14	57	18	46	29	45	32
	16	138	8	70	18	61	22	57	21	56

EXPERIMENT 3.2

Response Matrices for Individual Subjects - Inter-trial Interval 5 Seconds

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	290	48	121	49	120	55	110	62	127	43
	80	257	48	124	39	130	53	117	56	113
B1B	372	17	180	16	163	31	165	30	157	39
	23	365	17	180	35	162	48	149	53	143
B1G	301	89	164	33	168	30	133	64	91	107
	65	331	56	139	74	124	46	150	27	168
B2R	259	97	127	43	122	49	111	60	91	88
	31	312	11	162	21	151	18	160	18	153
B2B	353	47	178	22	156	44	145	55	105	95
	42	355	31	169	30	170	29	171	36	164
B2G	376	24	175	25	166	34	154	46	136	64
	63	337	28	172	55	145	46	154	74	126

B2W	309	87	151	47	140	58	106	87	112	86
	140	253	67	128	60	136	67	132	64	132
E1R	368	8	178	10	175	12	173	15	168	19
	10	365	6	181	14	174	28	159	35	152
LARGE MS										
G1R	351	49	166	34	137	62	132	67	93	107
	59	339	31	169	69	131	72	128	56	144
G1B	343	53	148	50	137	63	137	61	144	53
	73	321	26	173	25	173	45	153	76	124
G2R	370	30	159	41	174	26	179	21	172	28
	70	329	59	141	146	54	137	63	149	50
G2B	326	74	133	67	115	85	103	97	93	107
	125	275	52	148	64	135	70	130	79	121
G2G	371	27	179	20	133	67	109	90	100	100
	19	381	28	170	74	125	51	147	60	139
G2W	331	68	166	34	155	44	139	61	161	39
	44	355	58	141	72	128	111	89	118	81
MAMMILLARY										
D1R	315	58	152	34	128	61	114	79	96	93
	37	332	20	170	28	162	23	165	23	160
D1B	320	79	163	36	165	35	162	38	157	43
	164	235	86	113	123	76	125	75	131	69
D1G	304	80	127	59	114	77	117	74	113	79
	122	252	59	126	82	110	89	99	105	84
D2R	342	15	164	18	154	25	140	43	120	54
	28	324	18	160	46	133	39	135	47	131
D2B	382	10	181	15	165	33	167	30	158	40
	7	384	2	193	12	186	11	183	17	178
D2G	352	48	175	25	157	43	165	35	164	36
	22	378	24	176	57	143	76	124	87	113
D2W	293	107	133	67	100	100	86	114	79	121
	136	264	89	111	77	123	70	130	65	135
SHAM										
C1R	342	54	163	33	152	48	128	69	115	84
	21	372	22	174	35	165	45	152	31	168
C1G	273	35	131	25	135	26	133	26	148	7
	41	273	29	132	43	114	73	87	99	57
C2R	313	74	149	48	127	67	128	65	115	77
	38	343	74	116	79	115	86	106	100	93
C2B	330	51	172	22	105	89	101	90	70	122
	11	367	29	160	30	165	31	162	24	167

C2G	378	20	178	21	156	43	155	43	155	44
	14	381	25	173	32	168	48	151	66	132
C2W	346	40	146	48	113	79	113	80	50	142
	73	309	19	171	86	108	41	152	25	164

Response Matrices for Individual Subjects - Inter-trial Interval 15 Seconds

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	234	33	102	36	114	20	103	34	99	31
	53	226	26	112	33	107	30	111	33	108
B1B	323	19	165	7	165	10	157	11	159	10
	11	333	9	163	30	142	34	142	35	137
B1G	276	54	151	17	147	20	145	24	113	54
	12	325	19	147	39	132	30	140	20	150
B2R	279	27	135	18	130	30	127	32	124	32
	27	291	11	149	14	146	21	138	25	131
B2B	303	32	140	28	122	47	114	56	100	70
	35	303	24	144	28	144	42	129	47	121
B2G	293	51	148	27	154	17	165	18	145	30
	26	325	38	142	84	101	93	85	123	48
B2W	299	49	138	38	124	49	90	78	78	95
	63	280	47	127	42	130	42	126	35	135
E1R	320	1	159	3	146	16	141	17	147	16
	4	299	3	149	34	157	4	154	7	150
LARGE MS										
G1R	316	28	116	49	87	79	98	70	95	72
	24	324	7	161	9	163	34	140	62	113
G1B	326	14	155	12	161	9	142	29	150	18
	34	304	17	158	31	137	55	120	66	103
G2R	305	35	129	45	110	60	97	71	105	66
	52	295	26	144	63	110	68	108	77	93
G2B	292	47	100	73	65	106	53	119	52	123
	89	251	27	155	21	149	23	151	33	141
G2G	334	12	150	19	143	35	119	57	100	74
	26	323	19	156	93	78	67	105	63	108
G2W	290	43	129	42	130	38	129	38	137	33
	26	316	26	147	61	111	90	85	127	46

MAMMILLARY										
D1R	276	18	138	6	128	17	129	14	124	24
	17	278	10	140	13	133	13	131	20	126
D1B	211	71	118	24	118	23	113	24	108	33
	55	230	39	105	63	75	69	75	79	65
D1G	226	48	91	44	60	77	54	83	59	74
	38	234	24	114	33	99	30	105	32	104
D2R	257	23	132	13	113	31	109	31	99	42
	7	279	18	124	22	122	34	110	41	102
D2B	282	7	138	7	133	15	123	24	123	30
	3	296	1	151	5	140	13	136	12	131
D2G	286	23	148	10	134	24	140	19	125	21
	10	288	28	122	51	102	64	91	83	713
D2W	251	66	101	58	78	78	69	83	48	104
	65	233	50	103	49	104	50	106	42	108
SHAM										
C1R	269	45	142	15	130	29	109	52	110	51
	16	308	15	144	18	142	33	126	30	129
C1G	251	22	111	22	119	19	117	25	131	13
	26	260	15	128	45	99	59	84	78	66
C2R	269	60	132	30	102	56	103	60	79	81
	45	276	57	106	55	108	51	110	72	90
C2B	281	43	130	37	120	64	93	67	95	68
	5	319	12	154	26	137	32	127	53	114
C2G	326	20	151	22	135	38	135	41	141	37
	12	330	10	164	9	164	26	150	26	146
C2W	289	39	126	36	108	54	88	74	59	104
	31	297	32	128	41	124	35	129	16	151

Response Matrices for Individual Subjects - Inter-trial Interval 40 Seconds

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	218	84	99	56	101	54	101	54	95	62
	20	292	14	143	35	119	42	116	46	110
B1B	336	3	166	3	161	6	158	6	153	12
	1	343	5	165	7	165	11	164	25	148
B1G	297	30	151	17	155	11	154	16	122	47
	22	318	35	131	36	138	17	155	20	155
B2R	260	64	117	49	107	51	106	55	101	63
	51	266	30	130	45	117	40	122	47	113

B2B	297	39	155	17	140	29	125	40	113	55
	11	330	32	138	31	144	35	142	43	132
B2G	328	7	157	12	142	27	130	35	142	22
	36	306	31	144	41	129	61	112	88	84
B2W	330	20	154	17	146	23	125	48	106	62
	52	296	39	133	45	122	46	132	31	144
E1R	334	5	164	3	168	5	160	6	155	7
	1	343	3	169	8	161	7	162	24	148
LARGE MS										
G1R	281	50	148	16	125	41	116	46	90	73
	23	308	36	127	34	132	45	124	32	130
G1B	260	59	132	31	120	43	115	45	119	41
	35	285	14	144	33	128	42	117	68	94
G2R	312	17	149	20	146	23	129	40	115	49
	37	301	55	117	82	93	72	98	87	83
G2B	221	113	69	96	49	116	29	143	27	140
	39	309	20	153	12	159	10	161	13	161
G2G	307	23	152	18	96	74	83	81	68	99
	18	319	27	154	52	118	54	119	46	123
G2W	319	15	145	19	131	41	129	36	133	32
	40	296	28	138	47	119	58	107	91	78
MAMMILLARY										
D1R	313	17	157	7	133	33	122	43	109	52
	19	306	8	154	14	148	22	140	27	136
D1B	280	52	129	38	120	49	121	44	124	43
	139	194	57	111	66	108	77	95	97	69
D1G	219	101	118	41	108	55	110	51	130	33
	70	250	63	97	69	91	94	68	105	55
D2R	332	6	154	9	144	21	125	42	92	75
	17	318	16	155	41	127	54	121	35	134
D2B	369	1	176	5	176	8	169	13	162	22
	1	365	1	185	1	189	2	183	8	177
D2G	329	17	153	14	133	35	110	62	116	53
	29	319	23	145	51	128	50	119	59	117
D2W	263	70	125	45	92	78	78	87	58	109
	78	266	65	113	55	120	66	106	40	128
SHAM										
C1R	308	26	144	21	111	50	108	58	95	67
	11	314	4	157	10	155	24	138	23	142
C1G	268	42	130	26	115	39	124	33	129	24
	33	280	21	135	32	122	48	108	71	84

C2R	252	57	110	42	90	62	80	71	70	89
	62	248	62	93	65	90	57	98	33	119
C2B	303	29	145	17	94	73	109	63	87	80
	9	321	17	155	38	128	30	138	48	122
C2W	263	71	127	42	113	55	85	82	35	130
	28	321	11	163	36	136	22	146	12	160

EXPERIMENT 3.3

Response Matrices for Individual Subjects - Baseline, unfilled delay in Part 1

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	171	33	74	25	82	19	61	43	72	34
	20	191	13	91	26	80	22	84	29	77
B1B	222	9	111	5	102	15	98	16	101	17
	12	220	4	112	9	106	17	102	25	89
B1G	205	25	99	12	95	25	76	34	66	48
	37	191	26	88	36	82	19	92	22	92
B2R	163	32	78	13	78	20	65	32	50	46
	21	176	15	84	20	76	22	80	21	77
B2B	205	32	99	17	100	16	92	29	79	36
	10	222	16	107	22	99	26	95	22	92
B2G	229	11	118	5	114	9	98	23	98	23
	25	216	18	101	39	83	45	78	50	71
B2W	225	20	105	14	94	33	79	49	64	58
	34	210	31	88	27	90	38	86	51	70
E1R	227	6	113	6	112	11	104	18	97	20
	4	233	1	120	7	114	10	111	11	110
LARGE MS										
G1R	144	23	69	12	68	17	63	20	50	34
	19	148	15	71	17	69	27	58	20	64
G1B	130	29	74	9	67	16	64	16	65	17
	37	125	26	56	27	55	48	35	50	30
G2R	160	12	82	8	70	17	64	22	48	35
	18	156	28	56	37	51	34	55	38	47
G2B	125	54	27	61	52	37	15	69	5	82
	8	164	1	88	6	79	3	86	3	81
G2G	163	10	82	6	56	27	34	54	37	52
	6	165	10	76	20	67	19	66	16	70

G2W	144	20	70	16	53	34	58	22	65	18
	13	155	18	67	22	64	36	51	48	40
MAMMILLARY										
D1R	155	27	84	9	68	25	61	31	51	45
	11	181	6	89	11	87	13	81	15	81
D1B	195	33	81	32	49	65	44	66	49	65
	86	141	35	81	27	89	25	94	28	87
D1G	133	47	62	31	67	25	81	13	83	17
	65	128	36	60	44	49	60	35	66	32
D2R	215	5	101	6	97	12	96	14	86	23
	7	209	13	96	34	76	45	64	40	67
D2B	213	3	103	5	98	6	99	6	96	11
	4	210	1	106	3	105	3	106	2	107
D2G	214	23	102	14	99	21	87	31	101	24
	17	219	27	91	39	76	46	75	47	65
D2W	160	72	73	40	57	57	47	71	37	85
	66	167	42	72	35	83	28	91	19	95
SHAM										
C1R	204	32	100	17	79	38	75	43	62	58
	11	221	6	109	19	96	26	89	15	102
C1G	144	23	68	15	62	24	60	23	60	25
	10	160	14	76	17	65	15	72	26	59
C2R	142	19	64	16	51	30	38	42	21	64
	28	139	19	67	23	58	27	54	15	67
C2B	197	35	103	11	90	29	64	50	56	60
	3	225	5	112	29	85	24	90	25	90
C2W	189	52	84	38	84	33	59	66	38	84
	49	198	34	88	37	85	26	98	14	109

Response Matrices for Individual Subjects - Free food at beginning of each delay in Part 1

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	180	54	73	47	75	43	73	44	76	42
	37	199	24	94	28	91	39	78	41	77
B1B	110	5	47	9	41	17	40	14	44	11
	12	103	9	46	9	49	10	45	14	39
B1G	265	6	129	7	125	7	117	19	94	40
	6	257	7	126	12	116	22	103	29	102

B2R	173	71	73	40	63	58	60	58	57	64
	27	207	17	103	25	95	35	86	43	81
B2B	208	44	102	23	98	31	76	51	54	73
	24	228	16	116	40	91	24	107	23	104
B2G	227	31	107	19	90	38	95	35	91	43
	120	136	61	72	59	66	71	62	81	49
B2W	202	49	94	27	99	26	96	31	104	23
	61	192	28	96	55	70	71	51	80	46
E1R	270	1	133	1	127	2	128	5	111	14
	17	233	7	119	15	112	16	111	24	102
LARGE MS										
G1R	208	11	99	12	93	19	86	28	70	49
	21	183	24	84	30	77	20	87	29	85
G1B	182	30	89	14	89	18	74	31	77	27
	64	149	27	78	23	76	30	74	34	69
G2R	187	21	93	13	72	33	70	39	59	43
	55	157	24	82	48	63	57	49	64	42
G2B	124	93	53	52	45	64	23	85	21	90
	7	209	2	109	5	102	4	102	4	106
G2G	181	38	90	17	50	53	36	67	39	67
	18	192	8	98	12	97	18	94	17	95
G2W	177	35	78	25	77	24	69	36	72	31
	44	165	34	71	47	55	61	47	68	39
MAMMILLARY										
D1R	225	29	105	20	81	43	72	57	65	55
	35	216	23	107	22	110	24	105	43	82
D1B	266	7	129	9	99	31	131	7	131	9
	19	248	16	119	7	120	29	96	26	100
D1G	182	52	90	29	99	20	98	22	100	19
	68	170	57	64	67	53	84	36	89	33
D2R	202	42	103	20	82	39	72	51	73	49
	41	201	17	105	27	95	35	87	44	76
D2B	194	39	97	22	94	20	84	33	78	37
	1	237	2	117	11	107	9	108	14	105
D2G	231	18	119	8	105	23	118	17	104	24
	17	239	16	112	53	84	53	76	82	46
D2W	211	49	98	32	91	36	81	45	70	60
	44	213	18	107	40	92	56	80	54	75
SHAM										
C1R	234	22	114	16	102	28	86	40	69	55
	15	238	12	119	17	115	18	109	20	107

C1G	232	10	98	24	97	23	93	27	99	25
	71	174	65	57	74	49	70	52	86	33
C2R	197	26	101	15	75	39	73	40	63	45
	114	118	64	54	60	57	60	56	61	53
C2B	203	44	99	24	76	48	58	68	44	79
	15	231	5	117	38	83	25	96	23	98
C2W	225	25	100	22	94	30	81	44	69	55
	61	188	24	103	23	101	36	88	33	93

Response Matrices for Individual Subjects - Free food at end of each delay in Part 1

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
SMALL MS										
B1R	196	18	96	11	91	20	91	17	86	20
	152	71	77	34	74	41	82	31	83	27
B1B	196	29	96	17	76	34	70	43	71	41
	27	205	13	101	19	98	16	99	18	98
B1G	229	4	112	4	109	11	106	13	100	18
	103	133	51	68	54	66	68	52	54	66
B2R	51	160	31	80	20	85	26	85	29	77
	23	198	13	99	14	94	18	98	24	91
B2B	138	92	67	51	65	53	71	47	70	48
	130	108	66	52	64	54	68	51	72	48
B2G	165	84	76	49	65	56	55	68	55	70
	86	155	30	91	32	90	38	82	35	85
B2W	40	161	12	88	11	89	15	87	12	93
	16	195	4	99	10	98	12	89	8	93
E1R	135	4	67	5	66	5	67	6	61	11
	7	133	3	65	8	58	9	62	22	47
LARGE MS										
G1R	60	140	31	66	23	76	21	79	16	85
	12	188	16	83	15	85	12	88	13	87
G1B	193	0	98	0	98	0	100	0	97	0
	200	0	100	0	98	2	99	1	99	1
G2R	149	42	76	19	72	22	75	23	81	15
	128	66	67	30	65	31	78	20	79	20
G2B	22	182	7	96	7	95	2	100	3	101
	2	198	3	98	3	97	2	98	5	95
G2G	42	157	15	86	14	84	11	93	17	86
	12	187	6	94	11	88	8	92	9	91

G2W	171	18	86	9	83	13	87	10	82	16
	113	82	67	32	71	27	68	29	68	29
MAMMILLARY										
D1R	142	78	60	49	40	69	29	82	19	89
	61	166	28	85	20	89	15	100	13	100
D1B	203	43	87	18	15	89	29	84	61	63
	162	86	66	32	12	89	22	86	61	64
D1G	199	14	101	6	101	7	103	3	99	1
	151	70	78	32	81	28	96	16	106	5
D2R	57	154	15	91	21	84	16	94	24	80
	15	209	6	103	9	102	12	96	9	102
D2B	70	150	29	81	33	80	24	83	26	80
	1	222	1	113	4	107	5	111	5	109
D2G	240	4	121	2	111	13	112	13	109	15
	210	30	99	21	88	32	98	22	96	24
D2W	190	2	92	1	98	2	99	1	98	2
	200	3	101	1	100	2	99	2	98	3
SHAM										
C1R	43	156	19	86	6	101	13	96	8	98
	3	224	1	112	1	111	7	102	1	108
C1G	114	127	28	85	72	51	68	52	74	49
	81	162	18	99	67	44	65	52	68	51
C2R	75	125	44	55	32	69	28	77	22	76
	46	155	18	81	31	72	26	75	17	87
C2B	213	6	108	7	109	4	96	10	101	12
	182	46	95	20	96	19	88	24	94	25
C2W	202	1	94	14	94	3	100	2	102	2
	202	13	85	20	95	5	103	5	101	5

Response Matrices for Individual Subjects - Baseline, DRL 0 s in Part 2

	DELAY (s)									
	6.5		10.5		18.5		26.5		34.5	
RAT										
LARGE MS										
F1R	159	10	70	11	58	26	61	21	66	19
	24	149	9	75	8	80	19	66	26	59
F1B	141	21	70	14	72	12	71	11	79	3
	43	117	22	60	16	67	39	42	68	13
F1G	146	12	73	7	72	6	67	12	62	17
	10	148	5	72	6	73	9	72	17	61

F2R	137	21	65	14	49	29	58	21	56	21
	3	156	3	77	9	70	15	64	19	59
F2B	153	16	70	15	65	21	51	35	30	53
	6	168	2	84	14	70	17	68	8	77
F2W	155	2	76	1	64	14	65	10	68	7
	41	114	28	51	28	51	36	44	51	27
SHAM										
E1G	192	14	99	6	87	16	96	9	102	3
	48	161	29	76	38	71	57	48	82	21
E2R	133	33	72	12	60	24	54	29	58	26
	2	168	2	83	10	70	12	75	25	61
E2B	161	14	74	12	74	11	61	23	69	19
	2	172	2	86	7	79	8	78	17	67
E2G	147	28	63	22	59	27	47	35	34	52
	12	161	7	78	23	60	22	62	22	66
E2W	147	5	67	10	57	19	51	23	42	35
	22	136	7	72	18	61	11	68	16	62

Response Matrices for Individual Subjects - Prelesion, DRL 4 s in Part 2

N.B. Delays were increased by a constant of 3 s (obtained from measuring actual delay lengths) to compensate for the increase in delay arising from the DRL 4 s requirement.

	DELAY (s)									
	9.5		13.5		21.5		29.5		37.5	
RAT										
LARGE MS										
F1R	217	183	103	97	81	119	85	115	48	152
	44	356	28	172	28	172	26	174	25	175
F1B	313	87	139	61	156	44	145	55	156	44
	51	349	33	167	65	135	82	118	118	82
F1G	375	37	187	19	184	23	190	16	179	26
	122	290	82	124	91	115	75	131	88	118
F2R	316	84	106	94	121	79	109	91	101	99
	20	380	13	187	31	169	51	149	80	120
F2B	311	89	137	63	82	118	64	136	38	162
	23	377	13	187	14	186	5	195	12	188
F2W	328	72	156	44	119	81	100	100	89	111
	110	290	86	114	78	122	55	145	62	138
SHAM										
E1G	302	98	152	48	146	54	155	45	148	52
	98	302	68	132	84	116	106	94	118	82

E2R	374	26	174	26	173	27	163	37	157	43
	7	393	8	192	25	175	55	145	74	126
E2B	333	67	153	47	145	55	151	49	137	63
	7	393	7	193	13	187	18	182	26	174
E2G	370	30	145	55	114	86	84	116	76	124
	67	333	41	159	50	150	30	170	30	170
E2W	291	109	129	71	135	65	104	96	98	102
	27	373	21	179	29	171	32	168	34	166

Response Matrices for Individual Subjects - Postlesion, DRL 4 s in Part 2

	DELAY (s)									
	9.5		13.5		21.5		29.5		37.5	
RAT										
LARGE MS										
F1R	309	91	144	56	130	70	123	77	112	88
	37	363	20	180	39	161	37	163	44	156
F1B	245	155	83	117	84	116	97	103	109	91
	98	302	41	159	48	152	73	127	98	102
F1G	316	94	159	46	167	38	161	44	154	51
	182	228	81	124	108	97	127	78	126	79
F2R	301	99	110	90	117	83	114	86	103	97
	45	355	31	169	62	138	63	137	65	135
F2B	280	119	131	76	64	139	60	141	25	182
	64	341	69	133	30	170	34	173	17	187
F2W	196	64	90	40	73	57	63	67	56	74
	93	167	52	78	44	86	44	86	38	92
SHAM										
E1G	278	117	121	76	118	88	147	43	144	46
	63	340	37	163	44	158	95	100	98	97
E2R	368	32	170	30	168	32	174	26	162	38
	18	382	23	177	40	160	62	138	78	122
E2B	371	29	185	15	164	36	146	54	135	65
	24	376	8	192	12	188	15	184	16	184
E2G	352	48	141	59	118	82	69	131	56	144
	32	368	29	171	26	174	24	176	25	175
E2W	320	80	150	50	145	55	141	59	141	59
	59	341	32	168	50	150	64	136	86	114

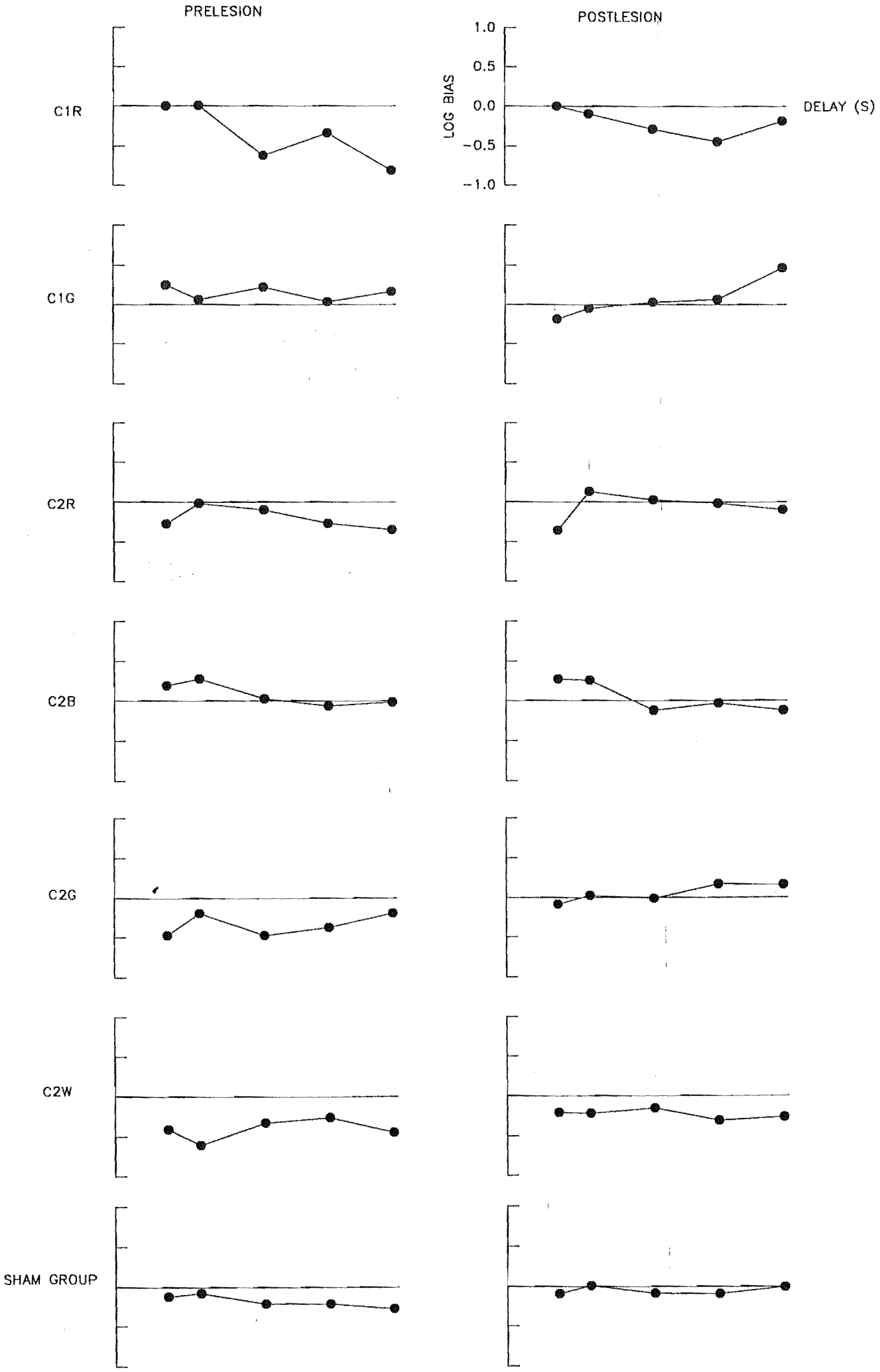
Response Matrices for Individual Subjects - Postlesion, DRL 4 s, FR 10 in Part 2

	DELAY (s)									
	9.5		13.5		21.5		29.5		37.5	
RAT										
LARGE MS										
F1R	185	5	92	3	87	5	86	8	87	7
	4	183	3	93	7	88	9	83	7	85
F1B	154	63	54	54	39	71	31	77	39	71
	26	190	4	104	17	92	20	87	28	82
F1G	191	25	90	18	91	17	95	13	89	19
	67	149	34	74	55	53	52	56	58	51
F2R	168	22	77	15	76	21	58	33	59	36
	14	173	17	76	28	71	27	67	28	67
F2B	202	18	97	13	66	44	44	66	19	91
	12	208	13	97	12	98	9	101	10	100
SHAM										
E1G	141	44	63	27	70	22	63	34	58	32
	49	139	14	78	33	59	38	55	39	54
E2R	207	6	100	6	99	7	92	15	97	10
	2	208	5	100	20	88	32	75	48	58
E2B	198	13	100	8	91	15	79	29	78	27
	10	202	3	101	4	102	2	105	5	102
E2G	201	18	94	15	73	37	60	49	44	65
	21	197	10	100	17	92	14	95	16	92
E2W	169	39	86	15	82	20	73	31	82	17
	39	161	17	85	25	78	34	67	37	68

ERRATUM

PAGE (LINE)	
7(24)	include (Brown, 1958)
13(2)	studies *occur* because
36(15)	do not *constitute* part
37(2)	trial-*dependent* (or working..)
41(4)	control group *nor* the
42(8)	*effects* can be
49(1)	performance *implicate*
57(22)	Log B=0.5(C1/E1xE2/C2)
59(3)	examined the effect of *a* delay *between*
65(10)	delete second *to*
69(9)	is more; delete *a*
70(10)	depends *upon* having
71(6)	sequence of arms *was*
82(2)	shown to reduce *the*
87(4)	calculation *of* bias-free
88(9)	*these* data *were*
88(13)	sessions *were*
91(11)	*appears* to decrease
92(12)	on the *right* and *left*
101(14)	neither the control group *nor* the MS..
106(7)	group *were* obtained
108(21)	Figure 2.8 (not '3')
120(10)	manipulations *of* variables
124(6)	bias-free *measures* of accuracy
126(3)	an increase *in the b* parameter
128(2)	*degrade*
137	header of Table 3.1 should be - ' .... dependence (DEP) indicates the degree of *dependence* between the two obtained parameters in a given function'.
146(2)	*Part 2* should read *Part 3*
148(3)	the Ms *group* was
152(2)	as *a* means
154(5)	smaller than *that*
155(2)	read *Log c* as *Log bias*
156(8)	observed *in* those studies
192(11)	Data *were* collected
193(7)	data *were* available
203(18)	already *engage* in
212(2)	delay-*independent*
216(10)	differences *among* subject groups
219(5-6)	served as valuable (delete *a*)
220(8)	switching *to* the side
225(5)	interference be demonstrated (delete *could*)
225(13)	human data *have* indicated
226(15)	is dependent upon the (delete *on*)
227(12)	on rats from *the* large
229(4)	were the same *as in the current trial*
229(7)	delete first *observed*
230(4)	perseverative *tendency* to
232(6)	compared to when (delete *the*)
234(17)	may be *an* important area
239(18)	need to *be* assessed
263-264	smallest lesion in 'shaded', largest lesion is shown by 'grid lines'

Bias Pre- and Post-lesion for Sham-Control group. Experiment 3.1 Part 2



Bias Pre- and Post-lesion for Large MS group, Experiment 3.1 Part 4